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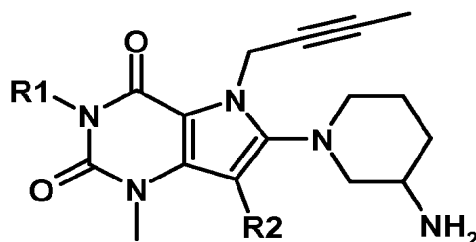
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(54) Title: **PYRROLO [3, 2 -D] PYRIMIDINES AS DPP-IV INHIBITORS FOR THE TREATMENT OF DIABETES MELLITUS**



(I)

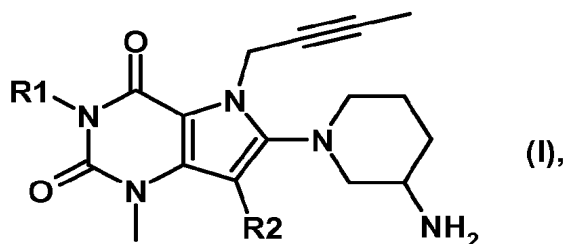
(57) Abstract: The present invention relates to substituted pyrrolo[3,2-d]pyrimidines of formula (I), wherein R1 and R2 are defined as in claim 1, including the tautomers, stereoisomers, mixtures and salts thereof, which have valuable pharmacological properties, particularly an inhibitory effect on the activity of the enzyme dipeptidylpeptidase-IV (DPP-IV).

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PYRROLO [3,2-D] PYRIMIDINES AS DPP-IV INHIBITORS FOR THE TREATMENT OF DIABETES MELLITUS

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The present invention relates to substituted pyrrolo[3,2-d]pyrimidines of formula (I)



including the tautomers, enantiomers, diastereomers, mixtures and salts thereof, particularly the physiologically acceptable salts thereof with inorganic or organic acids, which have valuable pharmacological properties, particularly an inhibitory effect on the activity of the enzyme dipeptidylpeptidase-IV (DPP-IV). It describes the preparation thereof and its use for the prevention or treatment of ailments or conditions which are connected with an increased DPP-IV activity or which can be prevented or alleviated by reducing the DPP-IV activity, particularly type I or type II diabetes mellitus. For this purpose, medicaments are provided which contain a compound of formula (I) or a physiologically acceptable salt thereof.

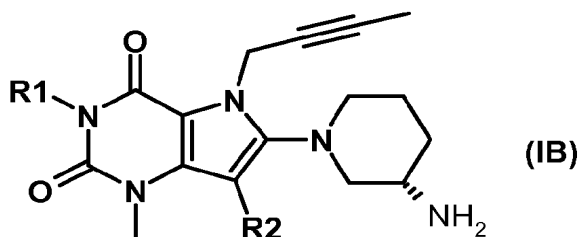
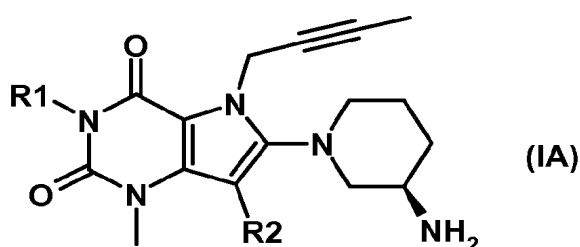
20 Pyrrolo[3,2-d]pyrimidine derivatives with an inhibitory effect on DPP-IV are known from WO 06/068163.

The compounds of formula (I) shown above include the tautomers, enantiomers, diastereomers, mixtures and salts thereof wherein R1 and R2 are defined as follows:

R1 represents ([1,5]naphthyridin-2-yl)methyl, (quinazolin-2-yl)methyl, (quinoxalin-6-yl)methyl, (4-methyl-quinazolin-2-yl)methyl, 2-cyano-benzyl, (3-cyano-quinolin-2-yl)methyl, (3-cyano-pyridin-2-yl)methyl, (4-methyl-pyrimidin-2-yl)methyl, or (4,6-dimethyl-pyrimidin-2-yl)methyl and

R2 represents hydrogen, methyl; hydroxy, methoxy; cyano, carboxy, methoxycarbonyl; aminocarbonyl, methylaminocarbonyl, dimethylaminocarbonyl; (2-methoxyethyl)-aminocarbonyl, (2,2,2-trifluoroethyl)aminocarbonyl;
 5 cyclopropylaminocarbonyl, cyclobutylaminocarbonyl;
 (cyclopropylmethyl)aminocarbonyl, (cyclobutylmethyl)aminocarbonyl; azetidin-1-ylcarbonyl, pyrrolidin-1-ylcarbonyl, piperidin-1-ylcarbonyl or morpholin-4-ylcarbonyl;

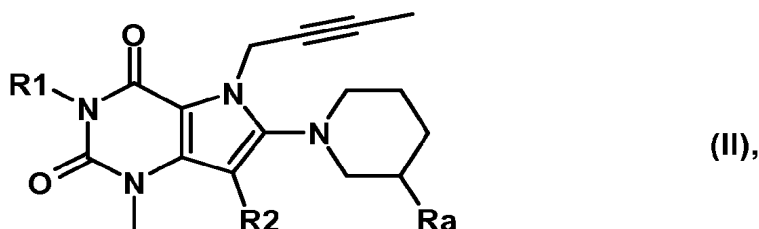
Preferred are compounds of formula (IA) or (IB)



wherein R1 and R2 are as hereinbefore defined, including the tautomers and salts thereof.

Most particularly preferred are the compounds of Example 1.

The compounds of formula (I) may be obtained by methods known *per se*. For example a compound of formula (II)



wherein R1 and R2 are as hereinbefore defined and Ra denotes an amino group protected by a protective group, is deprotected.

Preferred groups Ra are formylamino, acetylamino, trifluoroacetylamino, methoxycarbonylamino, ethoxycarbonylamino, tert.-butoxycarbonylamino and phthalimido, of which trifluoroacetylamino, methoxycarbonylamino, ethoxycarbonylamino, tert.-butoxycarbonylamino and phthalimido are particularly preferred.

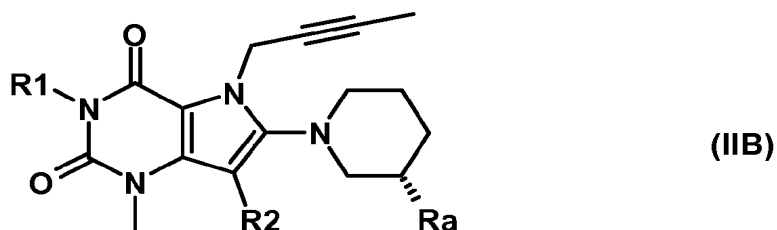
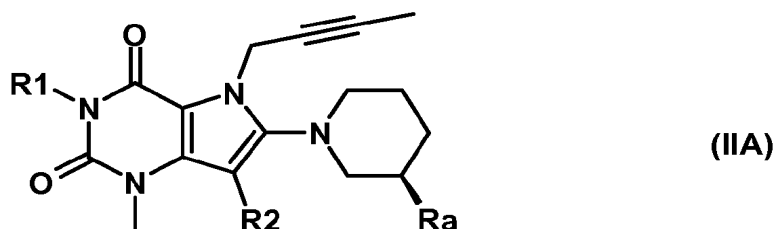
- 10 The cleaving of a tert.-butoxycarbonyl group is preferably carried out by treating with an acid such as trifluoroacetic acid or hydrochloric acid, optionally using a solvent such as methylene chloride, dioxane, methanol, ethanol, isopropanol or diethyl ether.
- 15 A formyl, acetyl, methoxycarbonyl, ethoxycarbonyl or trifluoroacetyl group is preferably cleaved by treating with an acid such as hydrochloric acid, optionally in the presence of a solvent such as acetic acid, at temperatures between 20 and 120°C or by treating with sodium hydroxide solution, optionally in the presence of a solvent such as tetrahydrofuran, methanol or ethanol, at temperatures between 0 and 100°C.

20

A phthaloyl group is preferably cleaved in the presence of hydrazine or a primary amine such as methylamine, ethylamine, ethanolamine or n-butylamine in a solvent such as methanol, ethanol, isopropanol, toluene/water or dioxane at temperatures between 20°C and the reflux temperature of the reaction mixture.

25

The invention further relates to the intermediate products of formula (II), particularly those of formula (IIA) and (IIB)



as shown, wherein R1, R2 and Ra are as hereinbefore defined.

- 5 The compounds of formula (I) obtained may be separated into the enantiomers and/or diastereomers thereof. Thus, for example, cis-/trans mixtures may be separated into their cis and trans isomers, and compounds with at least one optically active carbon atom may be resolved into their enantiomers.
- 10 Thus, for example, cis-/trans mixtures obtained may be separated by chromatography into their cis and trans isomers and the compounds of formula (I) obtained which occur as racemates may be separated by methods known *per se* (cf. Allinger N. L. and Eliel E. L. in "Topics in Stereochemistry", Vol. 6, Wiley Interscience, 1971) into their optical antipodes. Compounds of formula (I) with at least 2
- 15 asymmetric carbon atoms may be resolved into their diastereomers on the basis of their physical-chemical differences using methods known *per se*, e.g. by chromatography and/or fractional crystallisation, and, if these compounds are obtained in racemic form, they may subsequently be resolved into the enantiomers as mentioned above.
- 20 The enantiomers are preferably separated by column separation on chiral phases or by recrystallisation from an optically active solvent or by reacting with an optically active substance which forms salts or derivatives such as e.g. esters or amides with the racemic compound, particularly acids and the activated derivatives or alcohols
- 25 thereof, and separating the diastereomeric mixture of salts or derivatives thus

obtained, e.g. on the basis of their differences in solubility, whilst the free antipodes may be released from the pure diastereomeric salts or derivatives by the action of suitable agents. Optically active acids in common use are e.g. the D- and L-forms of tartaric acid or dibenzoyltartaric acid, di-o-tolytartaric acid, malic acid, mandelic acid, camphorsulphonic acid, glutamic acid, aspartic acid or quinic acid. An optically active alcohol may be, for example, (+) or (-)-menthol and an optically active acyl group in amides, for example, may be a (+)- or (-)-menthyloxycarbonyl.

Furthermore, compounds of formula (I) may be converted into the salts thereof, particularly for pharmaceutical use into the physiologically acceptable salts with inorganic or organic acids. Acids which may be used for this purpose include for example hydrochloric acid, hydrobromic acid, sulphuric acid, methanesulphonic acid, phosphoric acid, fumaric acid, succinic acid, lactic acid, citric acid, tartaric acid or maleic acid.

The compounds of formula (II) used as starting materials are either known from the literature or are obtained by methods such as those described for example in WO 04/018468, WO 05/085246 or WO 06/068163.

The compounds of formula (I) according to the invention and the physiologically acceptable salts thereof have valuable pharmacological properties, particularly an inhibiting effect on the enzyme DPP-IV. The ability of the substances including their salts to inhibit the DPP-IV activity can be demonstrated in an experiment in which an extract of the human colon carcinoma cell line Caco-2 is used as the DPP IV source.

The differentiation of the cells in order to induce the DPP-IV expression is carried out in accordance with the description by Reiher *et al.* in an article entitled "Increased expression of intestinal cell line Caco-2", which appeared in Proc. Natl. Acad. Sci. Vol. 90, pp. 5757-5761 (1993). The cell extract is obtained from cells solubilised in a buffer (10mM Tris HCl, 0.15 M NaCl, 0.04 t.i.u. aprotinin, 0.5% Nonidet-P40, pH 8.0) by centrifugation at 35,000 g for 30 minutes at 4°C (to remove cell debris).

The DPP-IV assay is carried out as follows:

50 µl of substrate solution (amido-4-trifluoromethylcoumarin (AFC)), final concentration 100 µM, are placed in black microtitre plates. 20 µl of assay buffer (final concentrations 50 mM Tris HCl pH 7.8, 50 mM NaCl, 1 % DMSO) is pipetted in. The reaction is started by the addition of 30 µl of solubilised Caco-2 protein (final concentration 0.14 µg of protein per well). The test substances under investigation are typically added prediluted to 20 µl, while the volume of assay buffer is then reduced accordingly. The reaction is carried out at ambient temperature, the incubation period is 60 minutes. Then the fluorescence is measured in a Victor 1420 Multilabel Counter, with the excitation wavelength at 405 nm and the emission wavelength at 535 nm. Dummy values (corresponding to 0 % activity) are obtained in mixtures with no Caco-2 protein (volume replaced by assay buffer), control values (corresponding to 100 % activity) are obtained in mixtures without any added substance. The potency of a test substance, expressed as the IC₅₀ value, is calculated from dosage/activity curves consisting of 11 measured points in each case.

In view of their ability to inhibit DPP-IV activity, the compounds of formula (I) according to the invention and the corresponding pharmaceutically acceptable salts thereof are suitable for influencing any conditions or ailments which can be affected by the inhibition of the DPP-IV activity. It is therefore to be expected that the compounds according to the invention will be suitable for the prevention or treatment of diseases or conditions such as type I and type II diabetes mellitus, prediabetes, reduced glucose tolerance or changes in the fasting blood sugar, diabetic complications (e.g. retinopathy, nephropathy or neuropathies), metabolic acidosis or ketosis, reactive hypoglycaemia, insulin resistance, metabolic syndrome, dyslipidaemias of various origins, arthritis, atherosclerosis and related diseases, obesity, allograft transplantation and osteoporosis caused by calcitonin. In addition, these substances are suitable for preventing B-cell degeneration such as e.g. apoptosis or necrosis of pancreatic B-cells. The substances are also suitable for improving or restoring the function of pancreatic cells and additionally increasing the size and number of pancreatic B-cells. Additionally, on the basis of the role of the glucagon-like peptides such as e.g. GLP-1 and GLP-2 and their link with DPP-IV inhibition, it is expected that the compounds according to the invention will be

suitable for achieving a sedative or tranquillising effect, as well as having a favourable effect on catabolic states after operations or hormonal stress responses or possibly reducing mortality and morbidity after myocardial infarction. Moreover, they are suitable for treating any conditions connected with the effects mentioned

5 above and mediated by GLP-1 or GLP-2. The compounds according to the invention may also be used as diuretics or antihypertensives and are suitable for preventing and treating acute kidney failure. The compounds according to the invention may also be used to treat inflammatory complaints of the respiratory tract. They are also suitable for preventing and treating chronic inflammatory bowel diseases such as e.g.
10 irritable bowel syndrome (IBS), Crohn's disease or ulcerative colitis and also pancreatitis. It is also expected that they can be used for all kinds of injury or damage to the gastrointestinal tract such as may occur in colitis and enteritis, for example.

Moreover, it is expected that DPP-IV inhibitors and hence the compounds according to the invention can be used to treat infertility or to improve fertility in humans or
15 mammals, particularly if the infertility is connected with insulin resistance or with polycystic ovary syndrome. On the other hand these substances are suitable for influencing sperm motility and are thus suitable for use as male contraceptives. In addition, the substances are suitable for treating growth hormone deficiencies connected with restricted growth, and may reasonably be used for all indications for

20 which growth hormone may be used. The compounds according to the invention are also suitable, on the basis of their inhibitory effect on DPP-IV, for treating various autoimmune diseases such as e.g. rheumatoid arthritis, multiple sclerosis, thyroiditis and Basedow's disease, etc. They may also be used to treat viral diseases and also, for example, in HIV infections, for stimulating blood production, in benign prostatic
25 hyperplasia, gingivitis, as well as for the treatment of neuronal defects and neuro-degenerative diseases such as Alzheimer's disease, for example. The compounds described may also be used for the treatment of tumours, particularly for modifying tumour invasion and also metastatisation; examples here are their use in treating T-cell lymphomas, acute lymphoblastic leukaemia, cell-based thyroid carcinomas, basal
30 cell carcinomas or breast cancers. Other indications are stroke, ischaemia of various origins, Parkinson's disease and migraine. In addition, further indications include follicular and epidermal hyperkeratoses, increased keratinocyte proliferation,

psoriasis, encephalomyelitis, glomerulonephritis, lipodystrophies, as well as psychosomatic, depressive and neuropsychiatric diseases of all kinds.

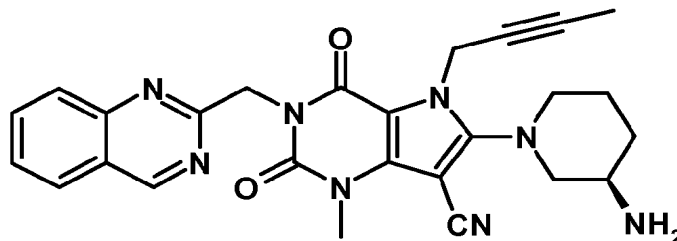
The compounds according to the invention may also be used in conjunction with other active substances. Suitable therapeutic agents for such combinations include for example antidiabetic agents such as metformin, sulphonylureas (e.g. glibenclamide, tolbutamide, glimepiride), nateglinide, repaglinide, thiazolidinediones (e.g. rosiglitazone, pioglitazone), PPAR-gamma agonists (e.g. GI 262570) and antagonists, PPAR-gamma/alpha modulators (e.g. KRP 297), PPAR-gamma/alpha/delta modulators, AMPK activators, ACC1 and ACC2 inhibitors, DGAT-inhibitors, SMT3 receptor agonists, 11 β -HSD inhibitors, FGF19 agonists or mimetics, alpha-glucosidase inhibitors (e.g. acarbose, voglibose), other DPPIV inhibitors, alpha2 antagonists, insulin and insulin analogues, GLP-1 and GLP-1 analogues (e.g. exendin-4) or amylin. Also, combinations with SGLT2 inhibitors such as T-1095 or KGT-1251 (869682), inhibitors of protein tyrosine phosphatase 1, substances which influence deregulated glucose production in the liver, such as e.g. inhibitors of glucose-6-phosphatase, or fructose-1,6-bisphosphatase, glycogen phosphorylase, glucagon receptor antagonists and inhibitors of phosphoenol pyruvate carboxykinase, glycogen synthase kinase or pyruvate dehydrokinase, lipid lowering agents, such as HMG-CoA-reductase inhibitors (e.g. simvastatin, atorvastatin), fibrates (e.g. bezafibrate, fenofibrate), nicotinic acid and its derivatives, PPAR-alpha agonists, PPAR-delta agonists, ACAT inhibitors (e.g. avasimibe) or cholesterol absorption inhibitors such as for example ezetimibe, bile acid-binding substances such as for example cholestyramine, inhibitors of ileac bile acid transport, HDL-raising compounds such as for example inhibitors of CETP or regulators of ABC1 or LXRAalpha antagonists, LXRBeta agonists or LXRAalpha/beta regulators or active substances for the treatment of obesity, such as e.g. sibutramine or tetrahydrolipostatin, dexfenfluramine, axokine, antagonists of the cannabinoid1 receptor, MCH-1 receptor antagonists, MC4 receptor agonists, NPY5 or NPY2 antagonists or β_3 -agonists such as SB-418790 or AD-9677 as well as agonists of the 5HT2c receptor, are possible.

It is also possible to combine the compounds with drugs for treating high blood pressure such as e.g. all antagonists or ACE inhibitors, diuretics, β -blockers, Ca-antagonists, etc., or combinations thereof.

- 5 The dosage required to expediently achieve such an effect is, by intravenous route, 1 to 100 mg, preferably 1 to 30 mg, and by oral route 1 to 1000 mg, preferably 1 to 100 mg, in each case 1 to 4 times a day. For this purpose, the compounds of formula I prepared according to the invention, optionally combined with other active substances, may be incorporated together with one or more inert conventional
- 10 carriers and/or diluents, e.g. with corn starch, lactose, glucose, microcrystalline cellulose, magnesium stearate, polyvinylpyrrolidone, citric acid, tartaric acid, water, water/ethanol, water/glycerol, water/sorbitol, water/polyethylene glycol, propylene glycol, cetylstearyl alcohol, carboxymethylcellulose or fatty substances such as hard fat or suitable mixtures thereof into conventional galenic preparations such as plain
- 15 or coated tablets, capsules, powders, suspensions or suppositories.

The Examples that follow are intended to illustrate the invention:

Example 1 1-methyl-3-[(quinazolin-2-yl)methyl]-5-(2-butyn-1-yl)-6-(3-(*R*)-amino-piperidin-1-yl)-7-cyano-2,4-dioxo-2.3.4,5-tetrahydro-1*H*-pyrrolo[3,2-*d*]pyrimidine



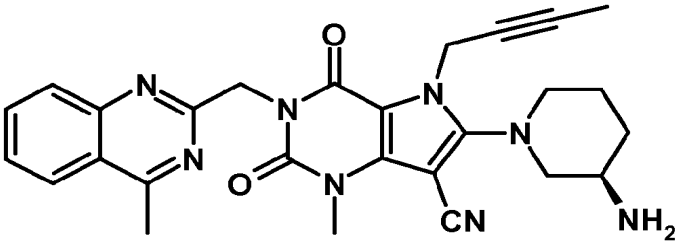
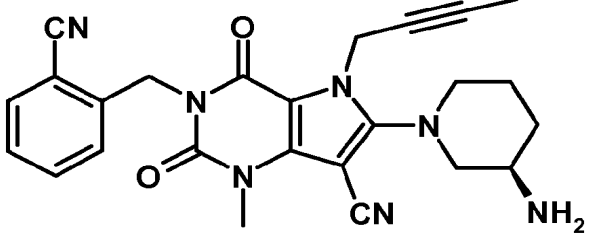
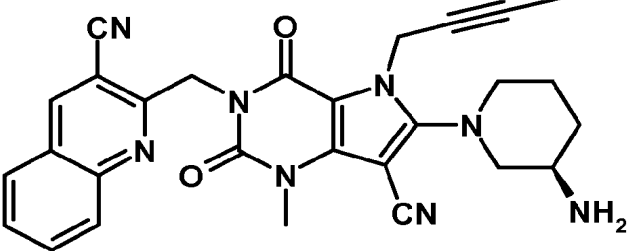
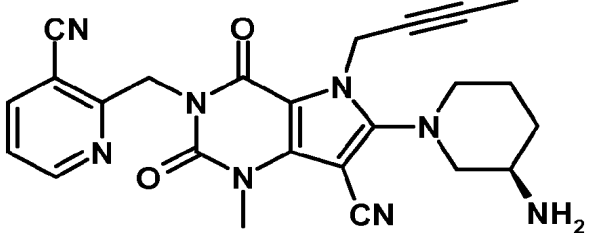
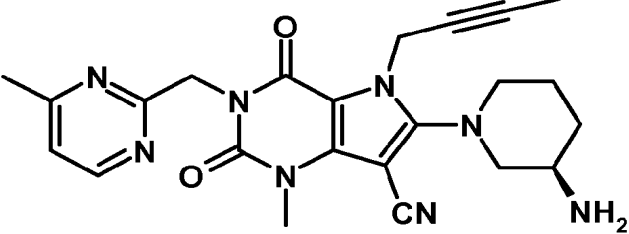
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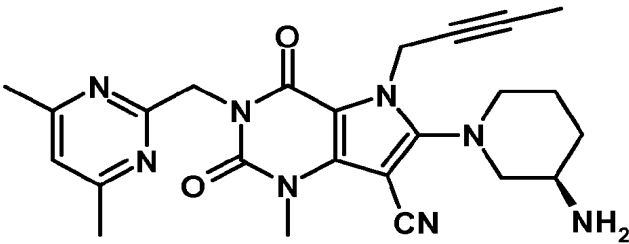
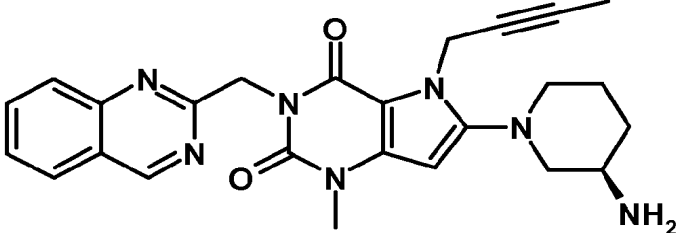
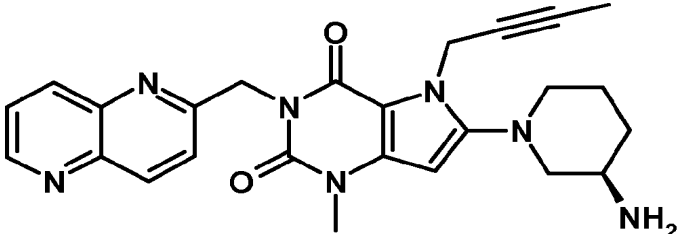
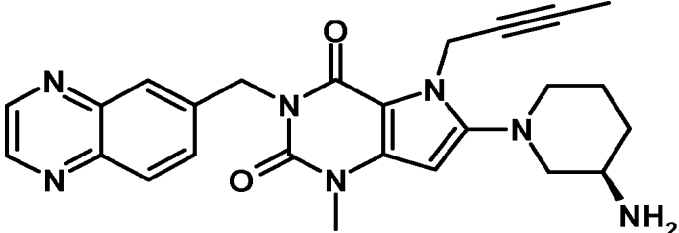
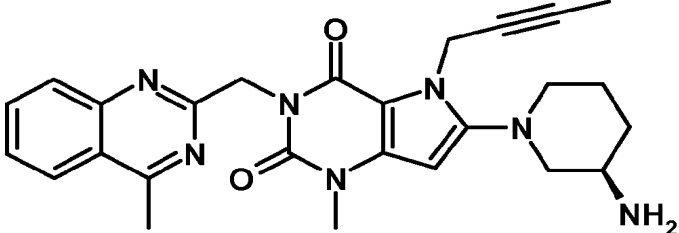
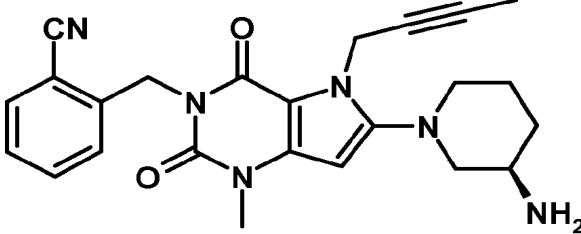
The title compound may be obtained by reacting 1-methyl-3-[(quinazolin-2-yl)methyl]-5-(2-butyn-1-yl)-6-[3-(*R*)-(tert.-butoxycarbonylamino)-piperidin-1-yl]-7-cyano-2,4-dioxo-2,3,4,5-tetrahydro-1*H*-pyrrolo[3,2-*d*]pyrimidine with isopropanolic hydrochloric acid.

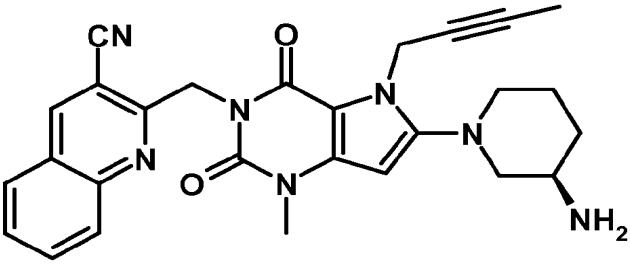
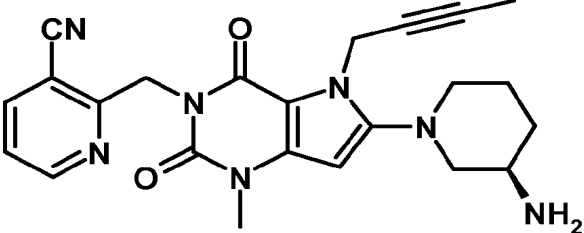
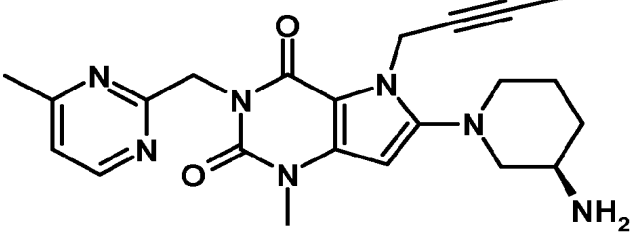
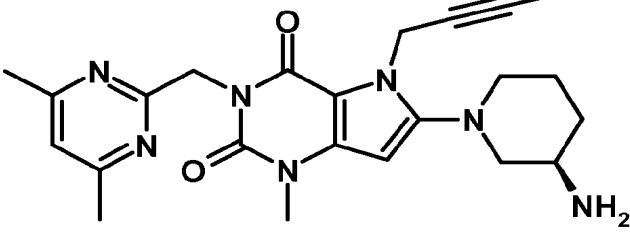
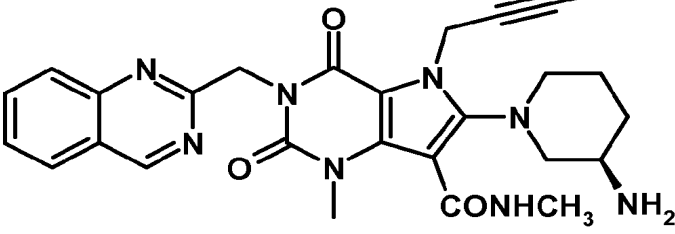
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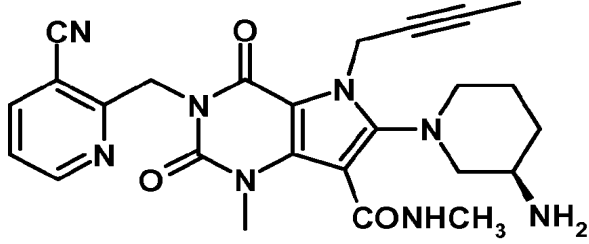
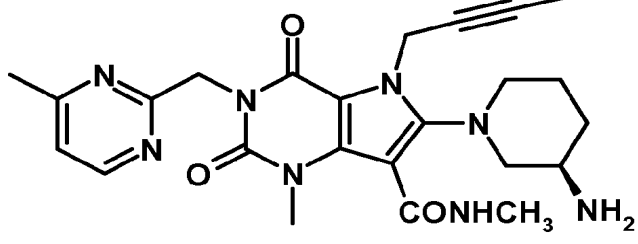
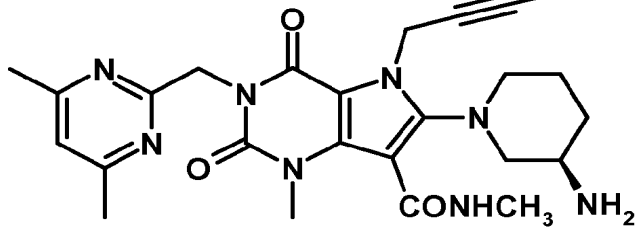
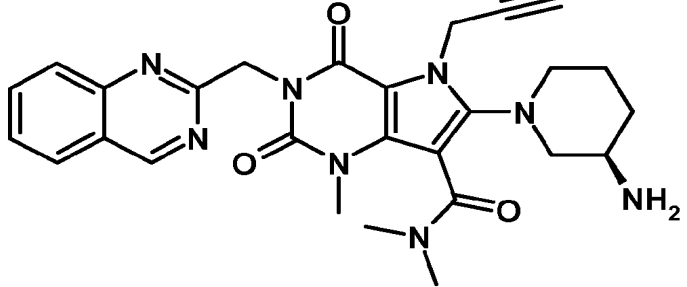
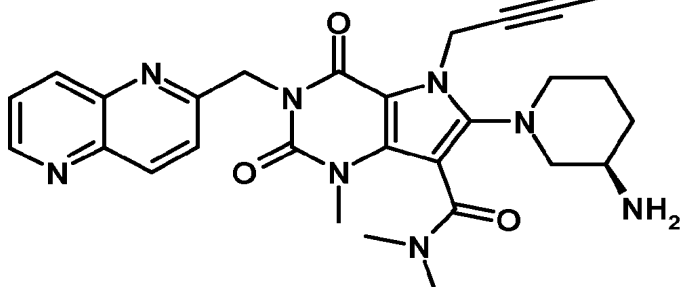
The following may be obtained analogously to Example 1 and other methods known from the literature:

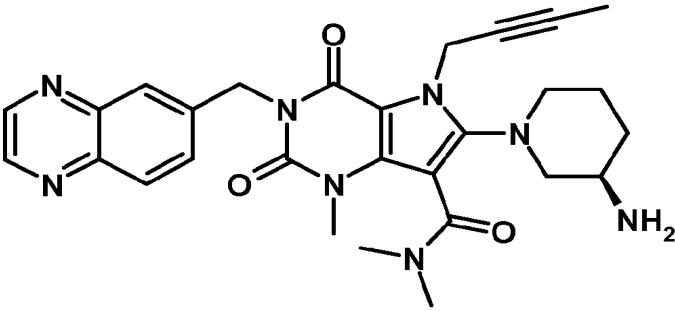
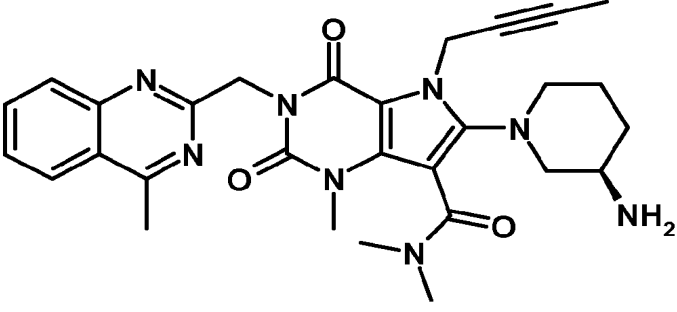
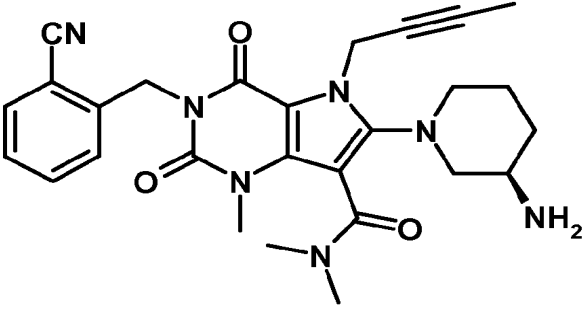
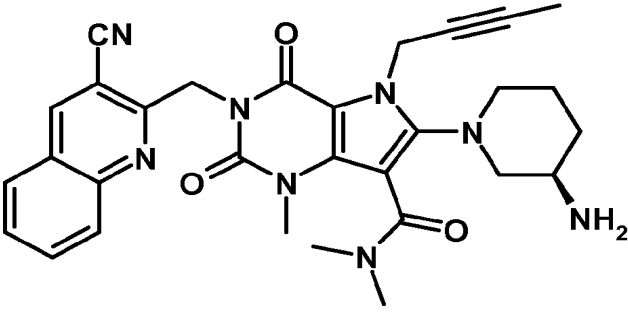
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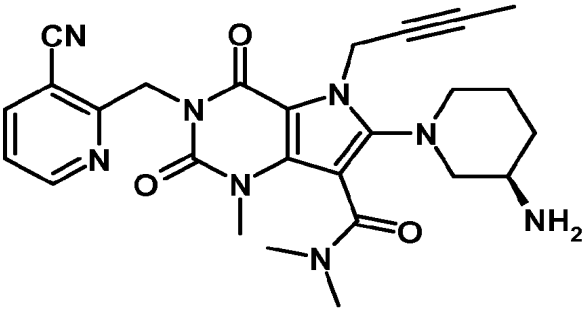
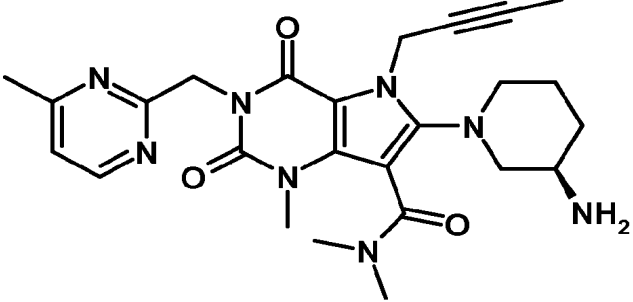
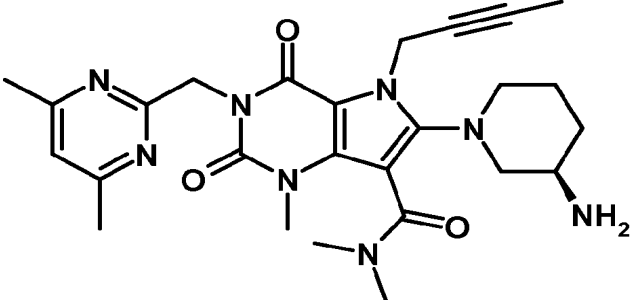
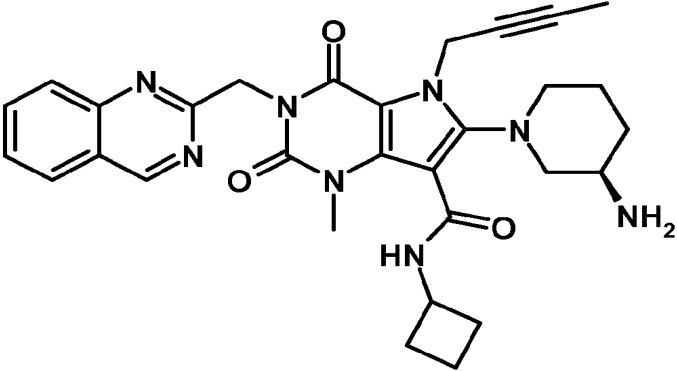
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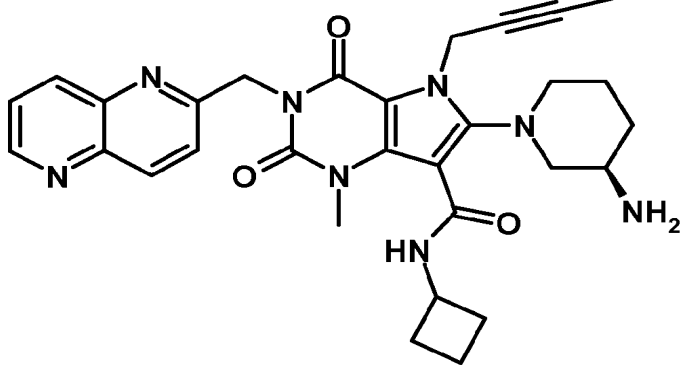
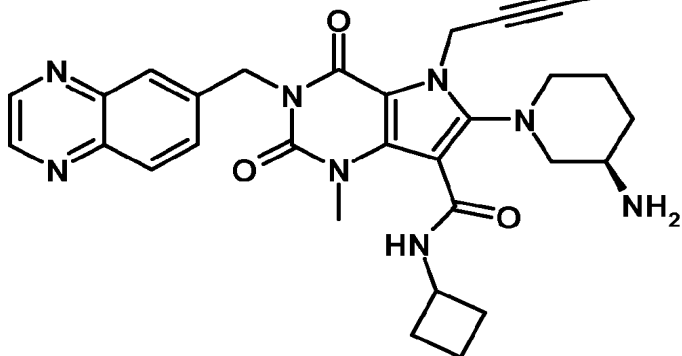
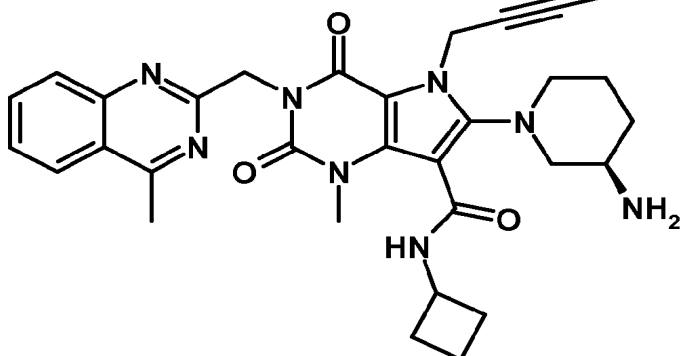
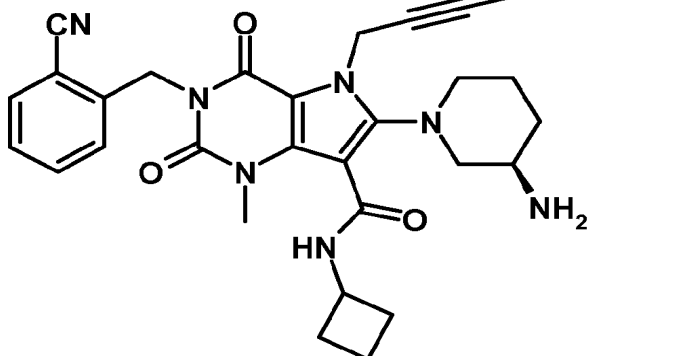
| Compound | Structure |
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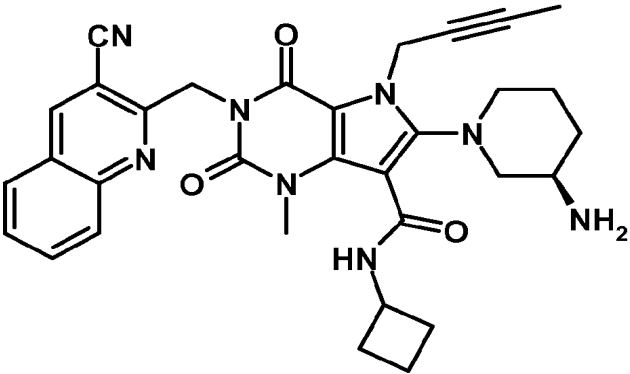
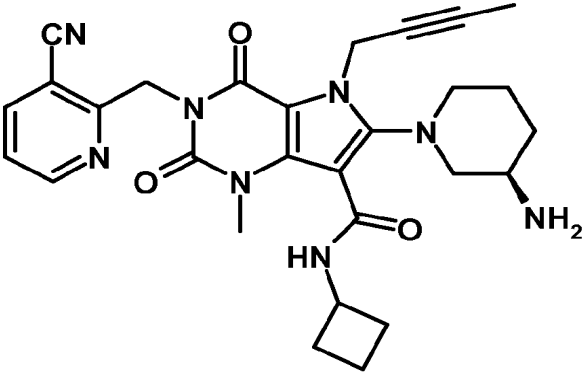
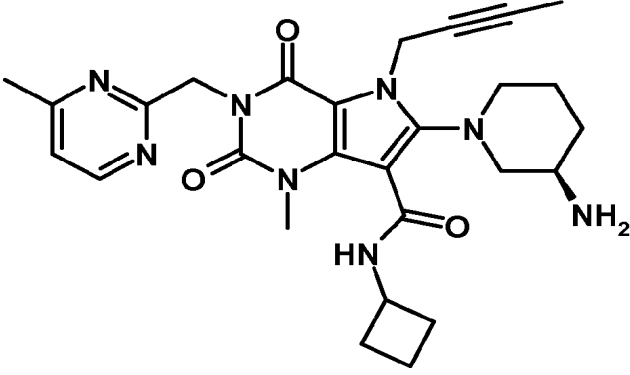
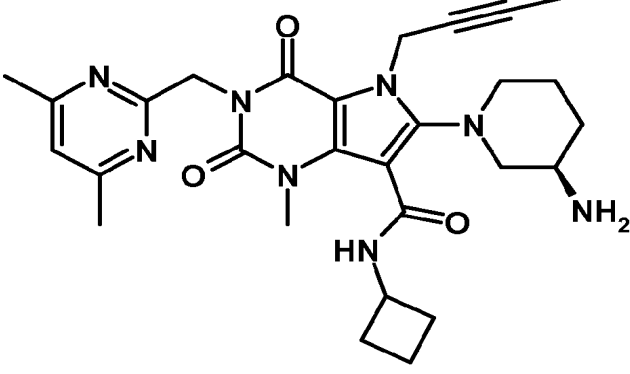
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| Compound | Structure |
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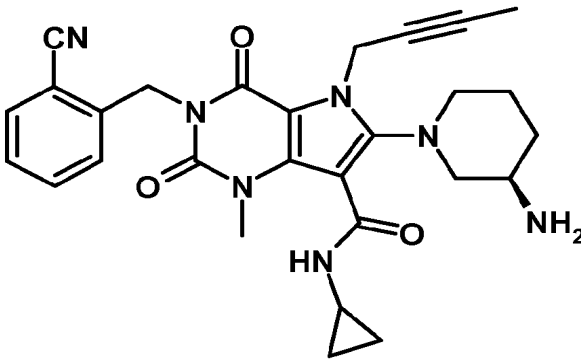
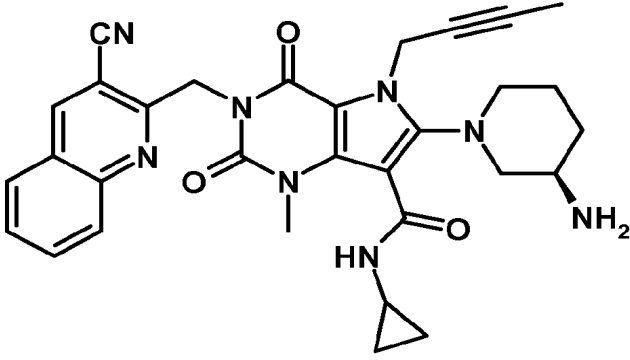
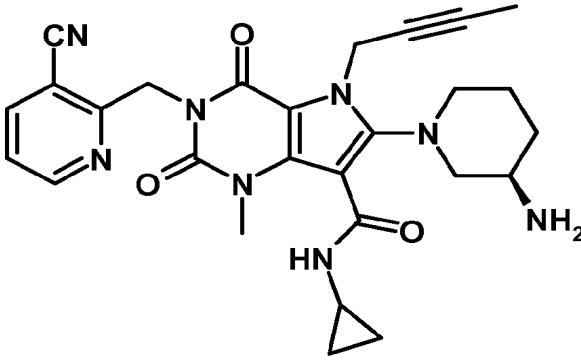
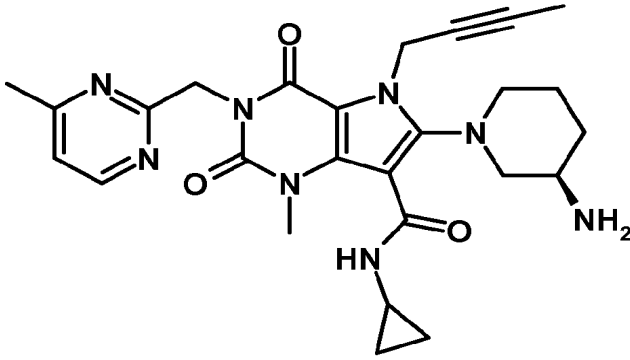
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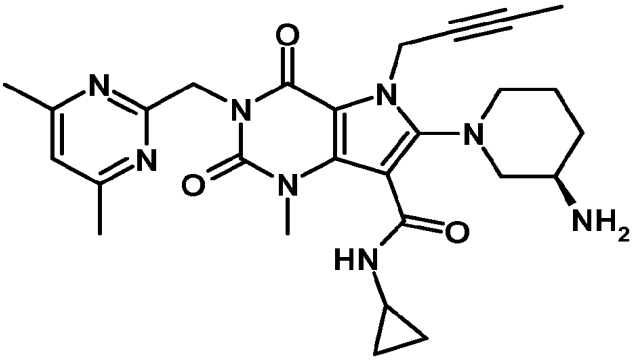
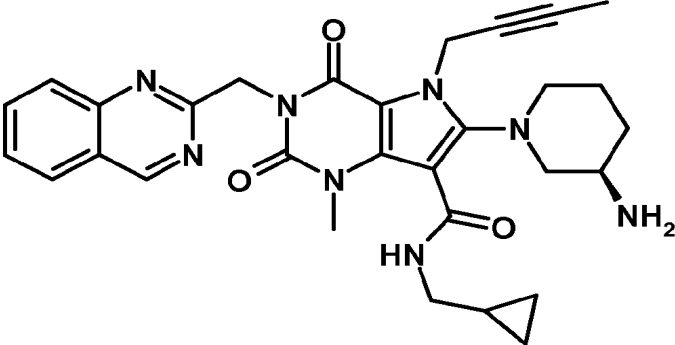
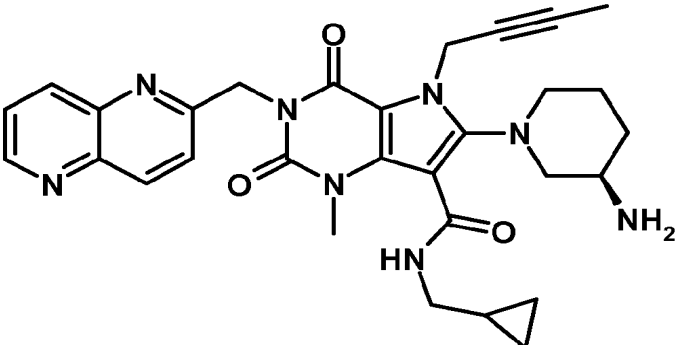
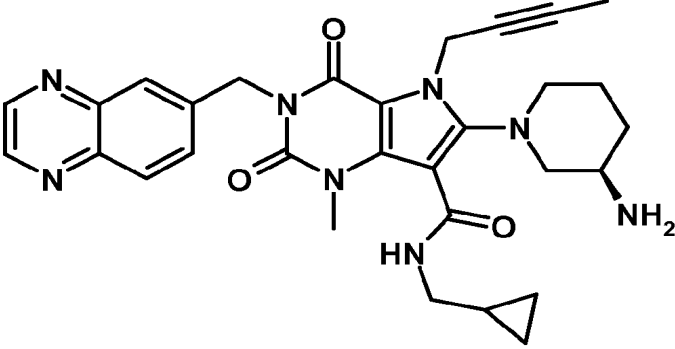
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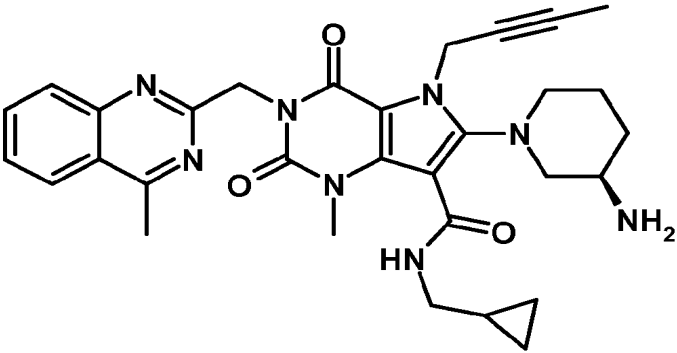
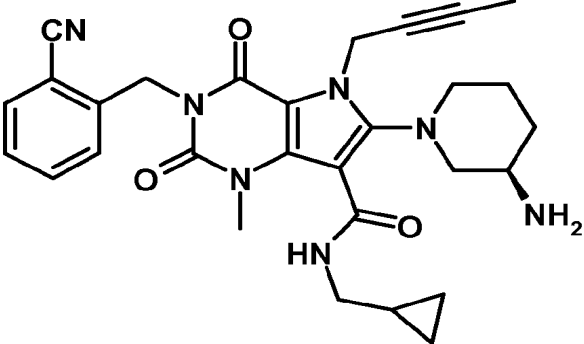
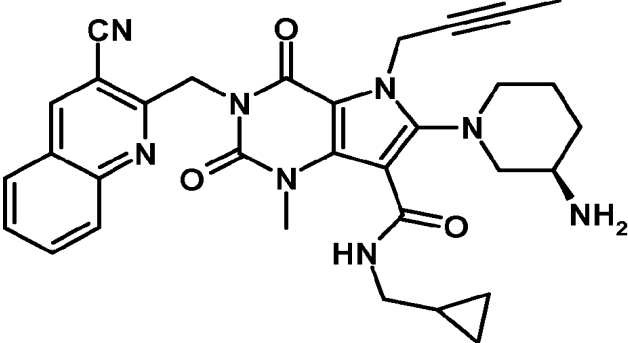
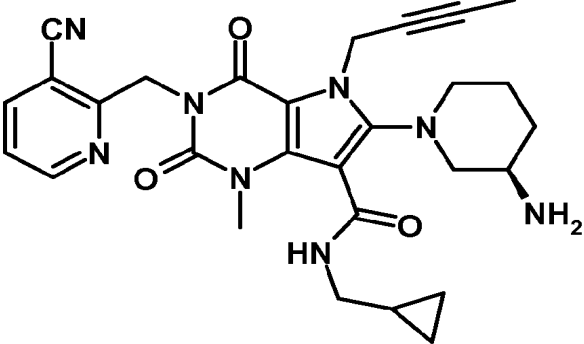
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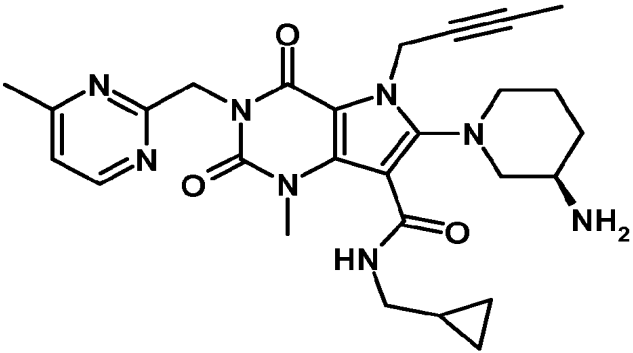
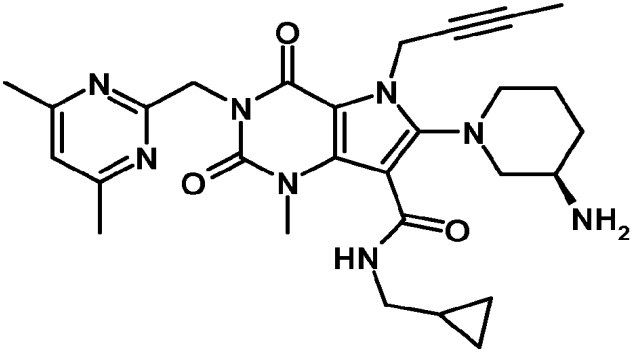
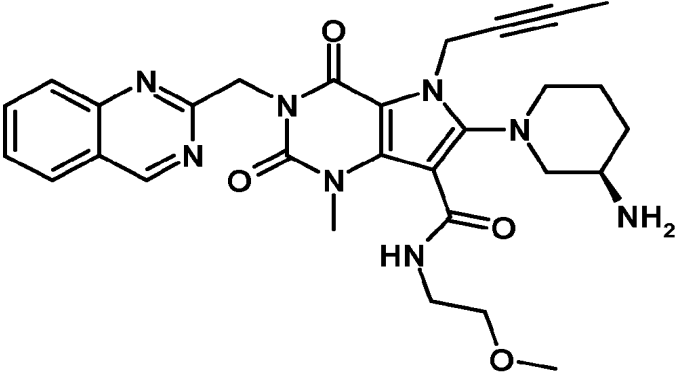
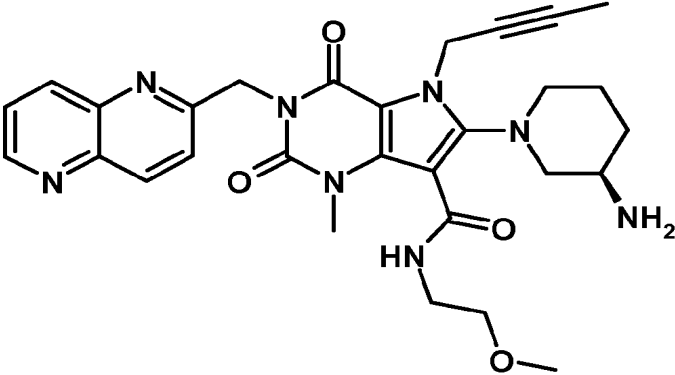
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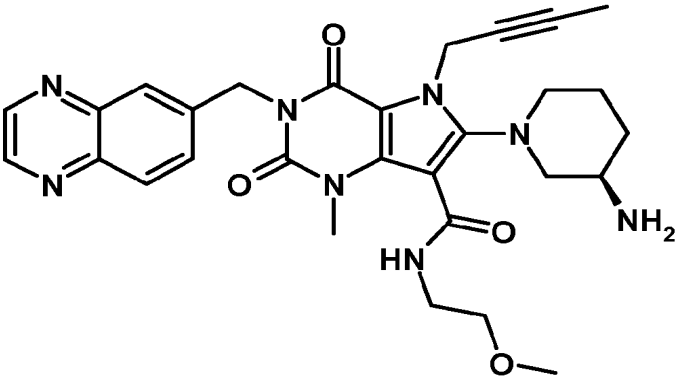
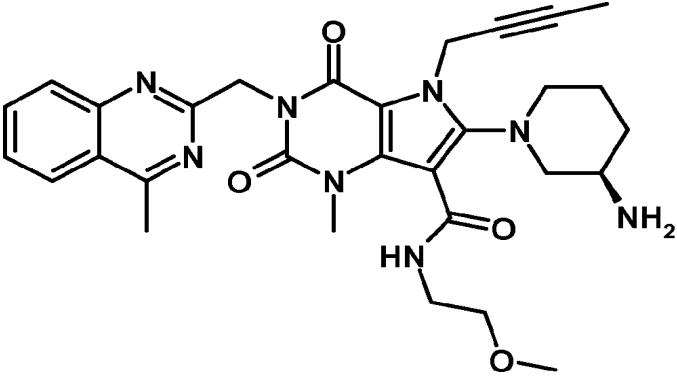
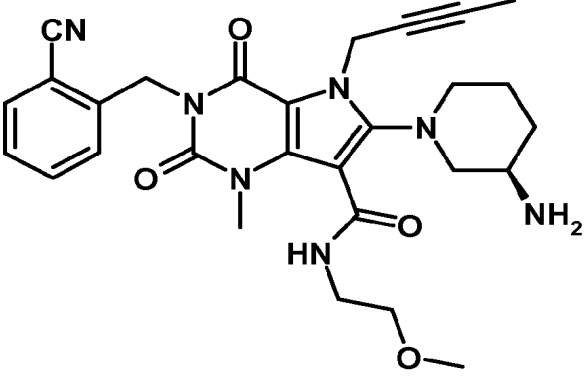
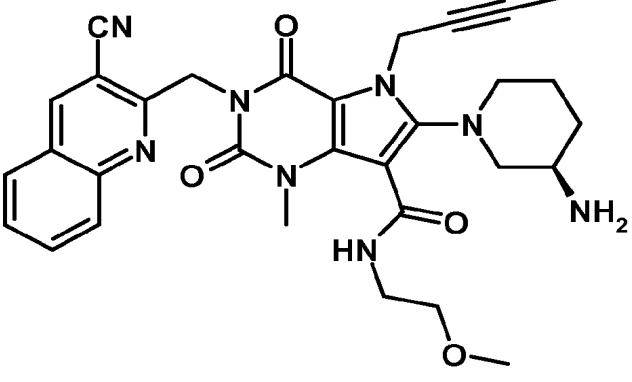
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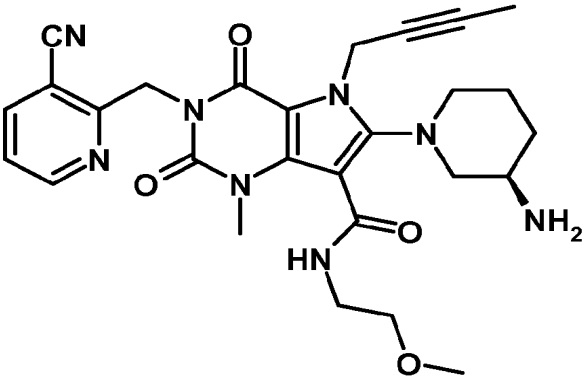
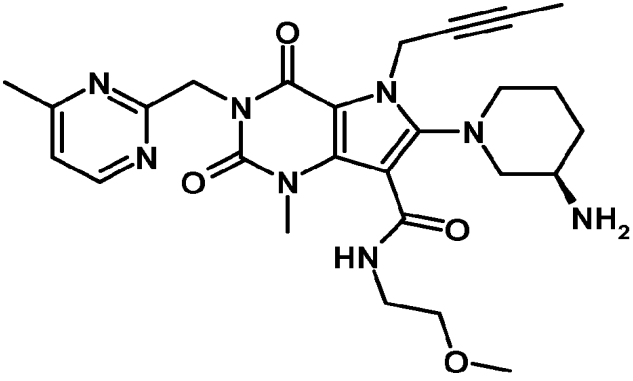
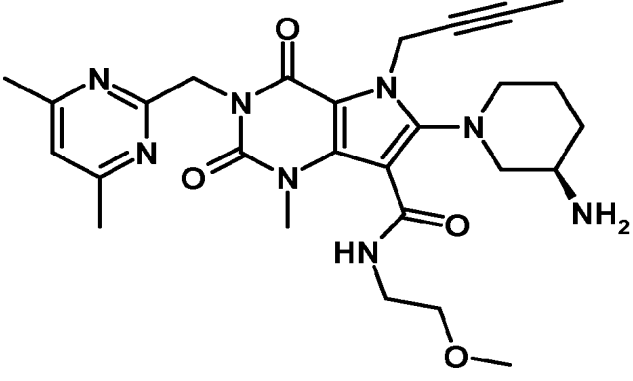
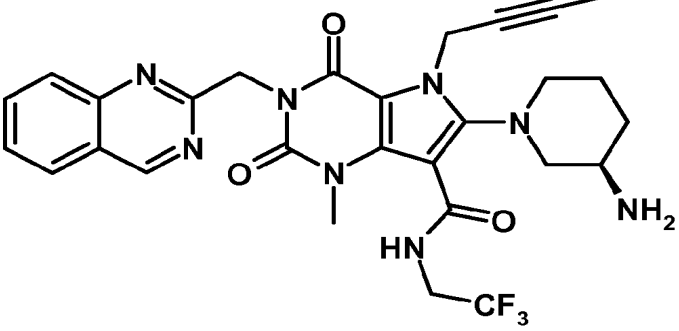
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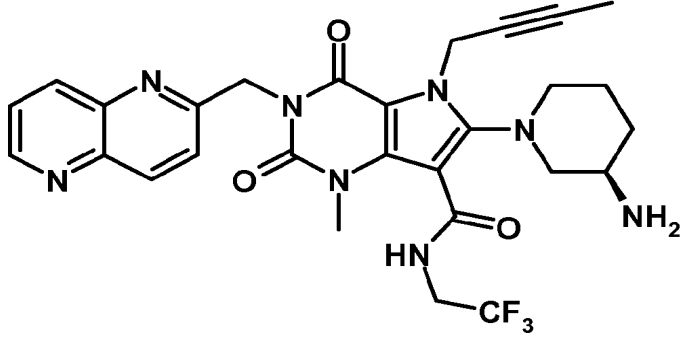
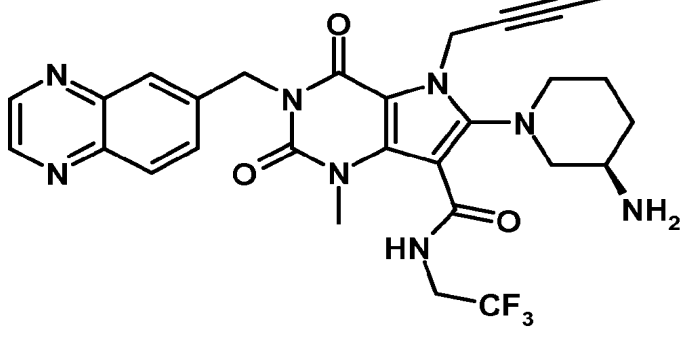
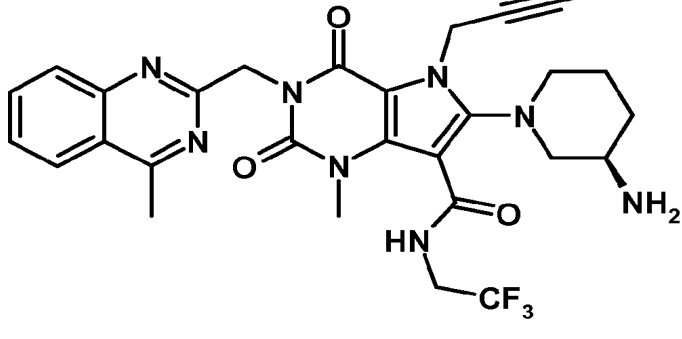
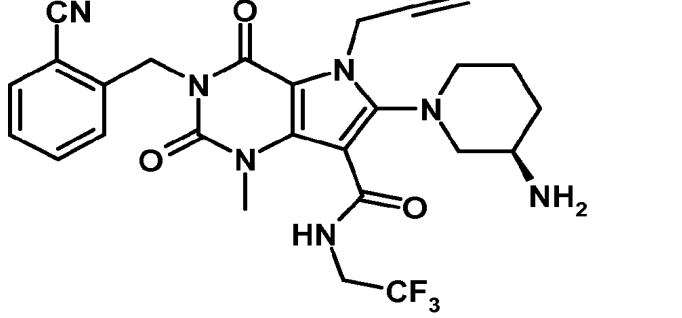
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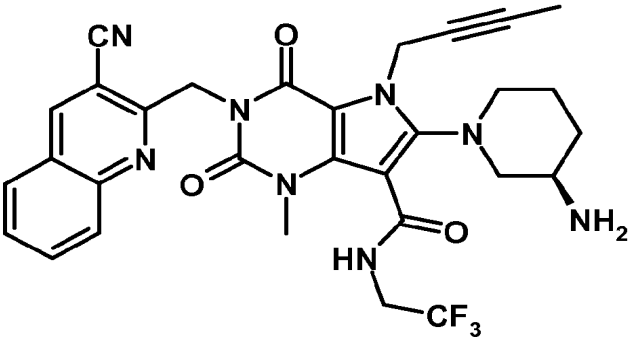
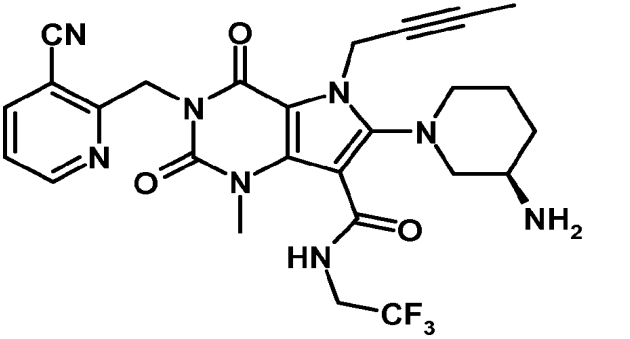
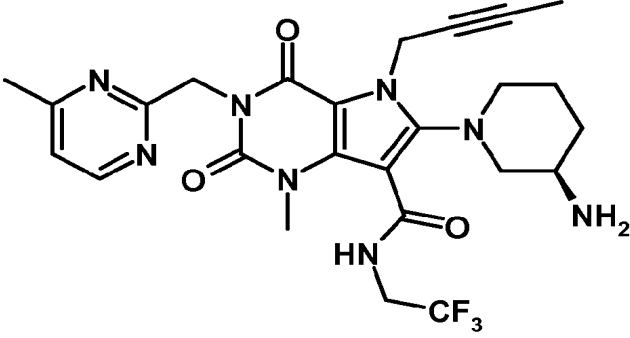
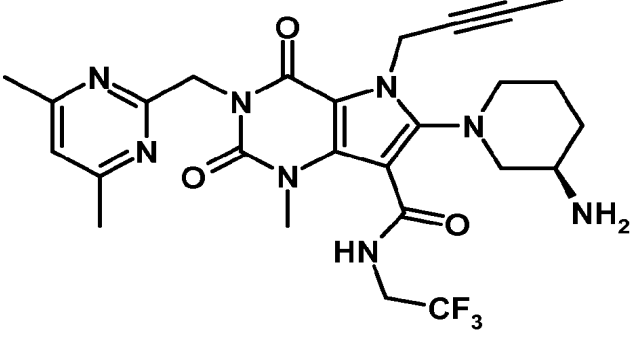
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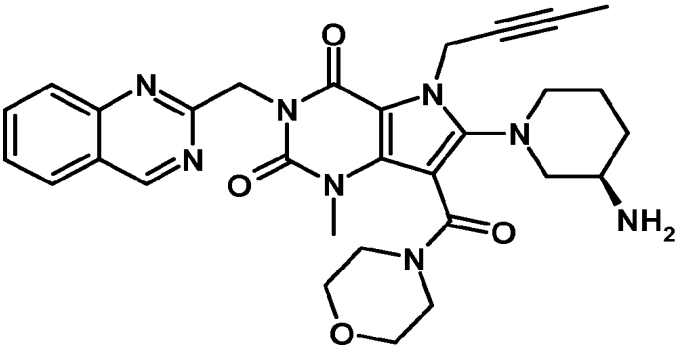
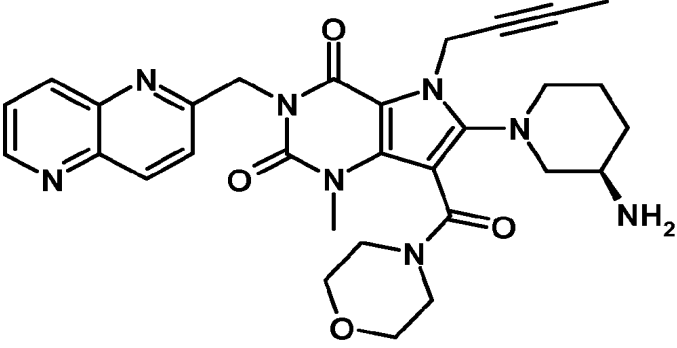
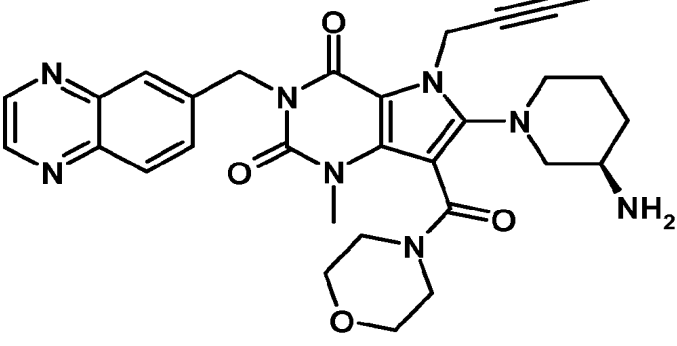
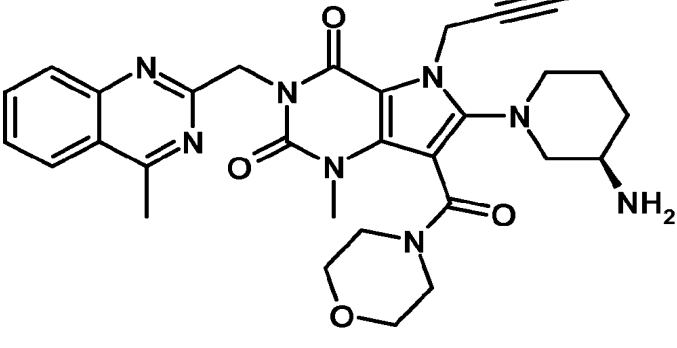
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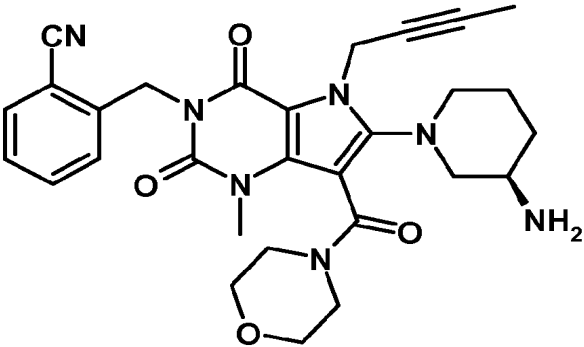
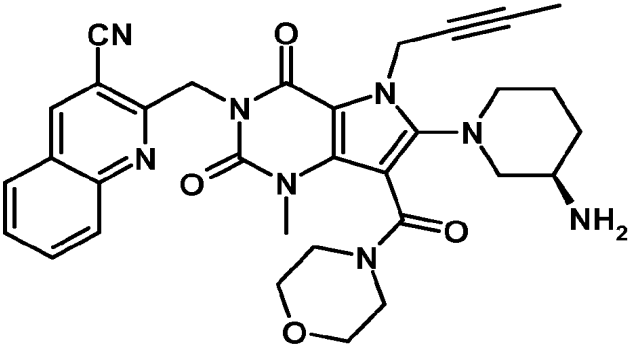
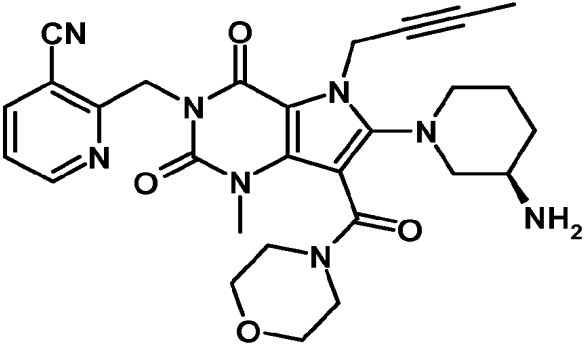
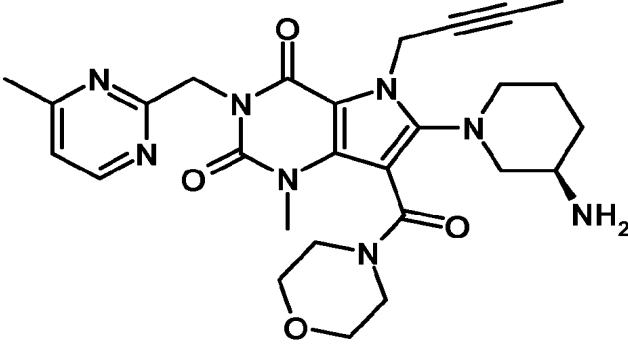
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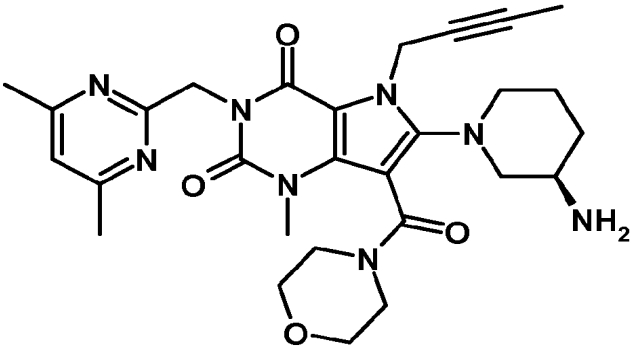
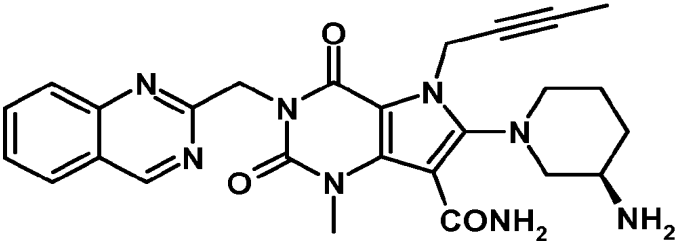
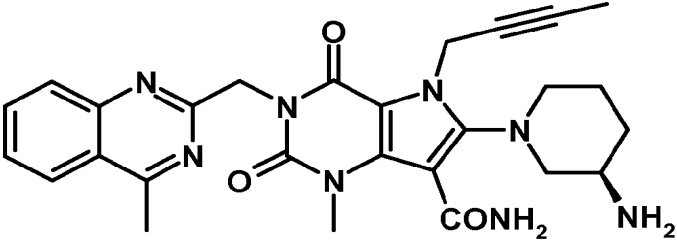
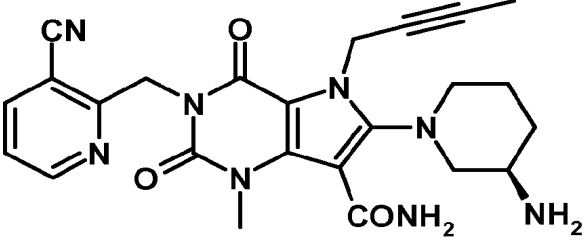
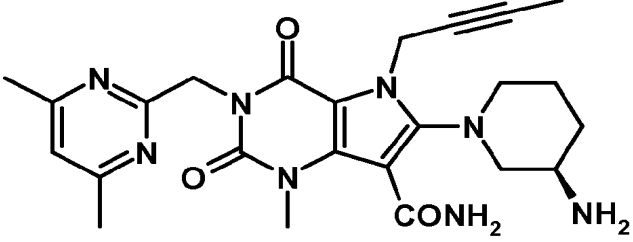
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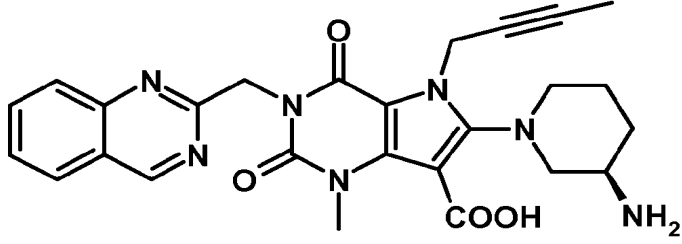
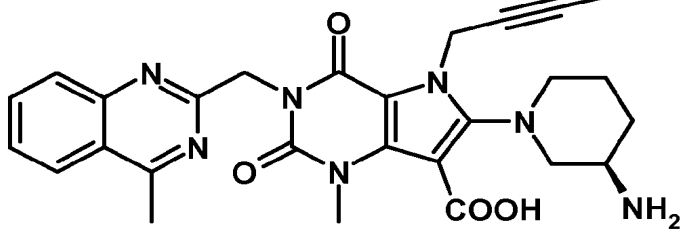
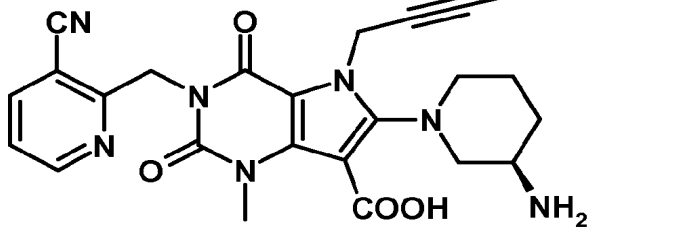
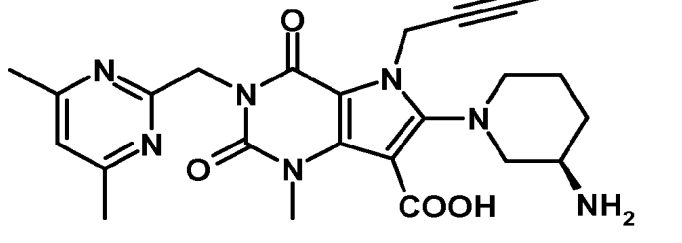
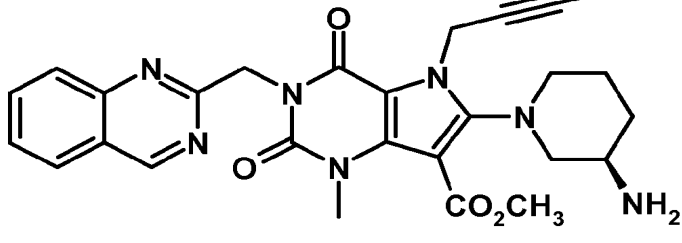
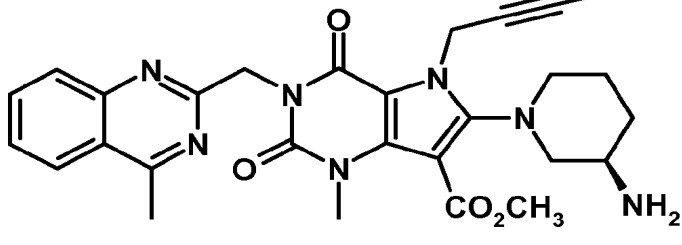
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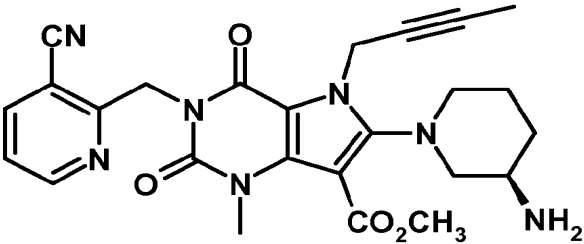
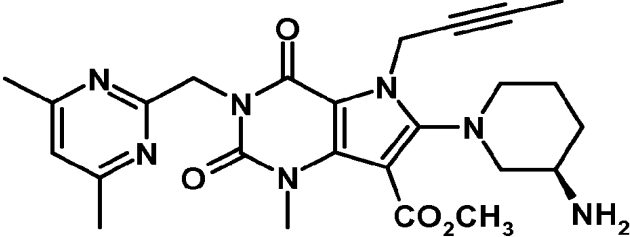
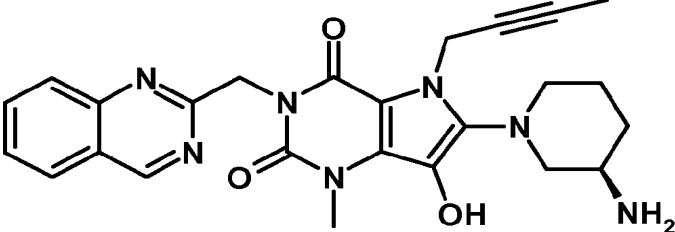
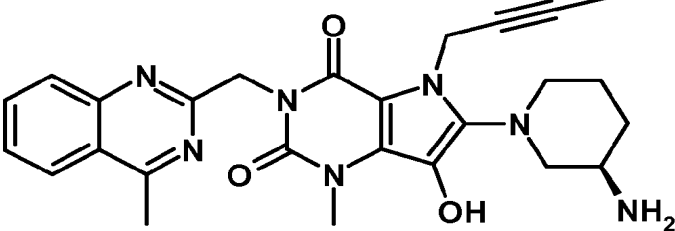
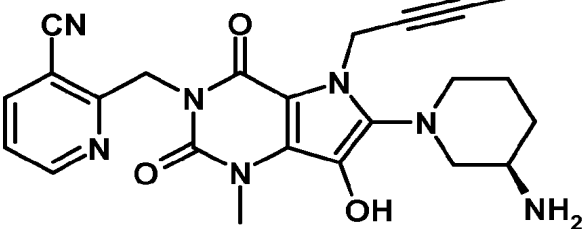
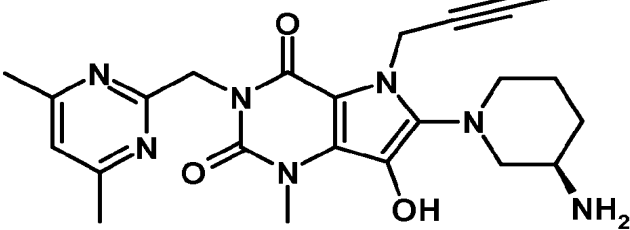
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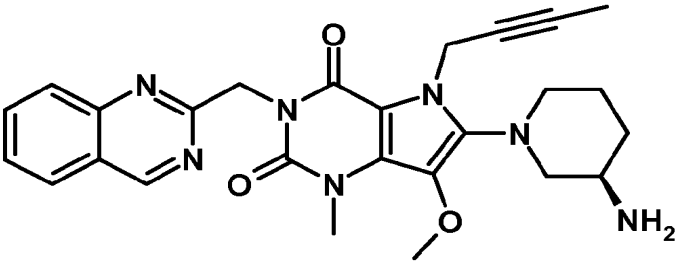
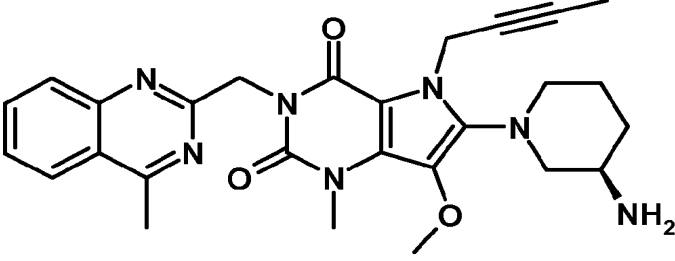
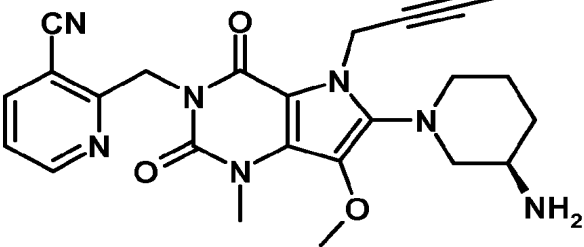
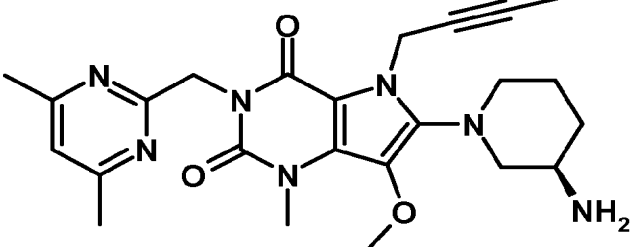
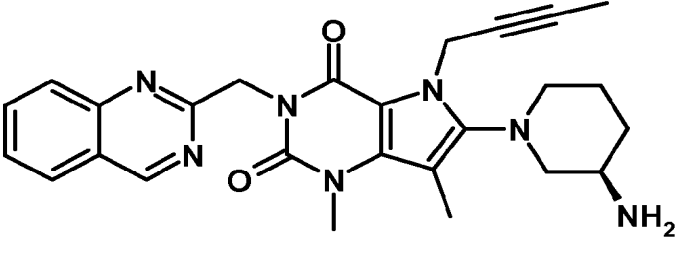
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| Compound | Structure |
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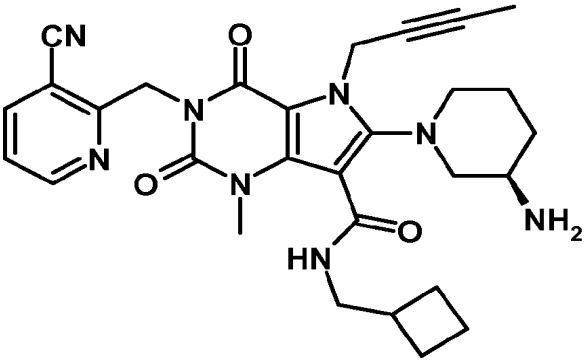
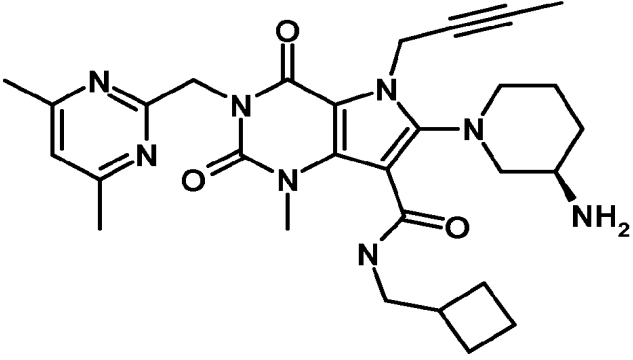
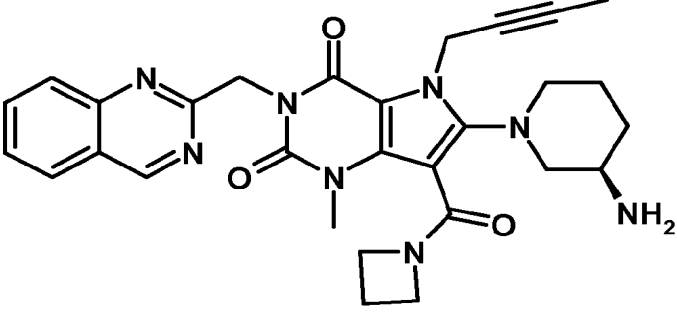
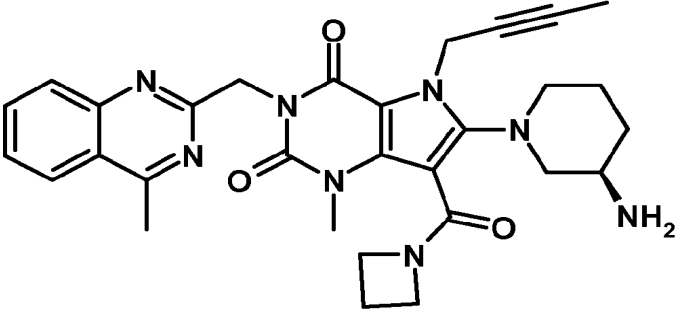
| Compound | Structure |
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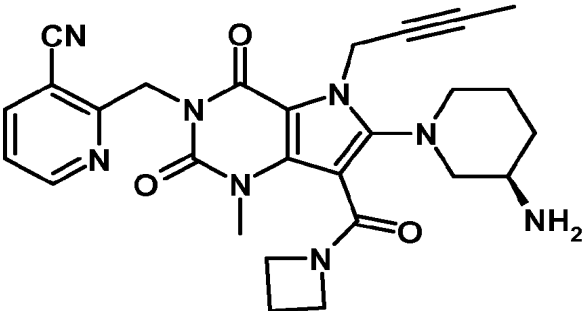
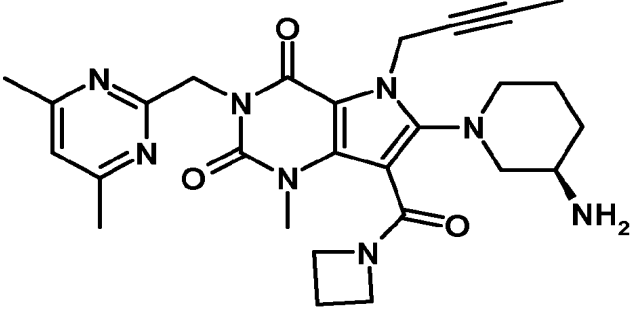
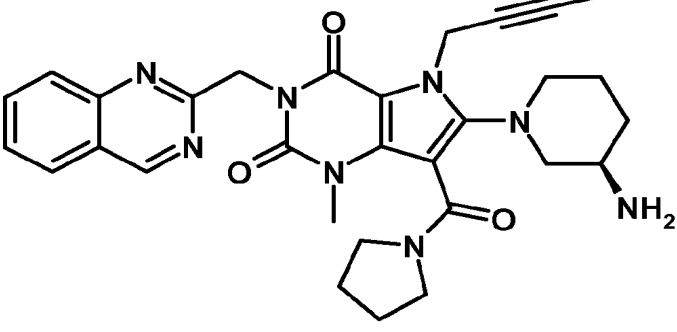
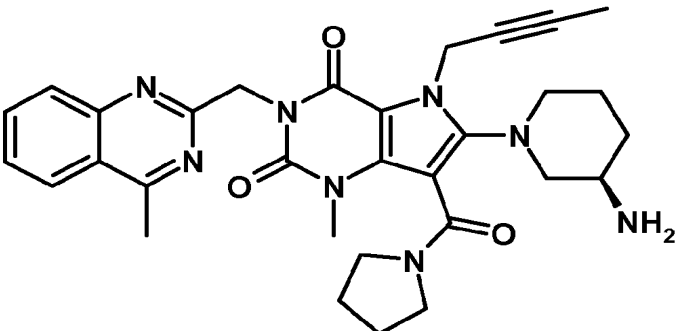
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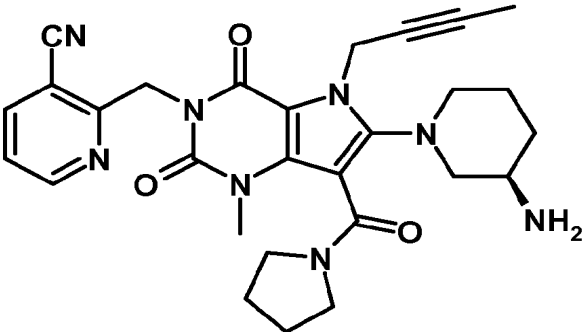
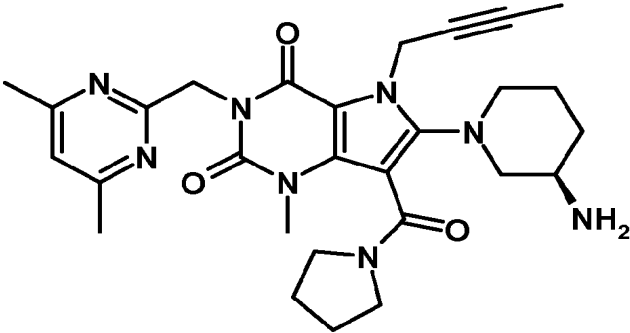
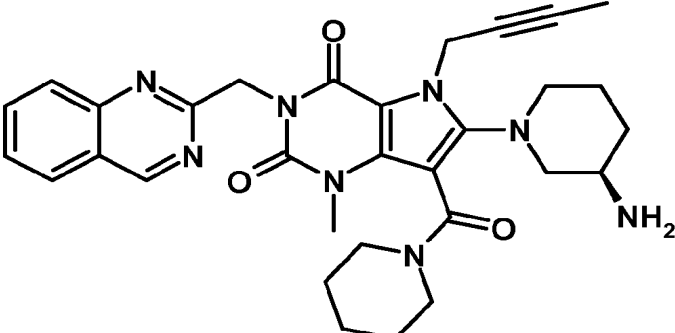
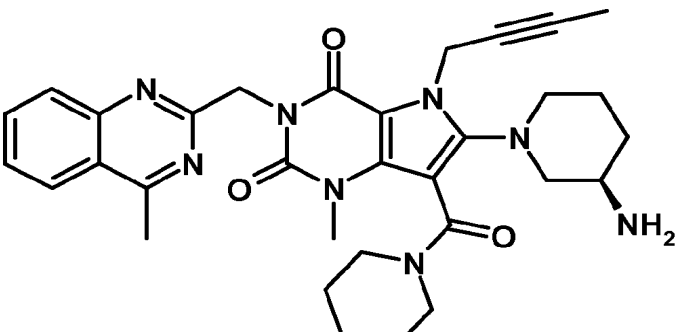
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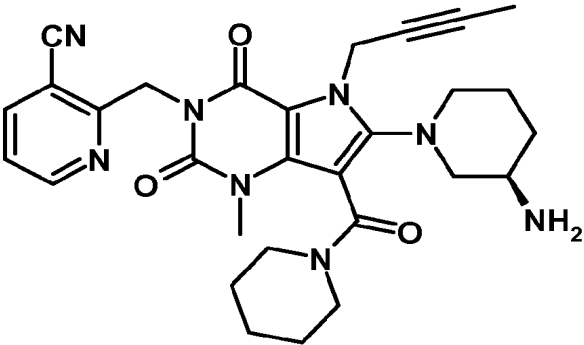
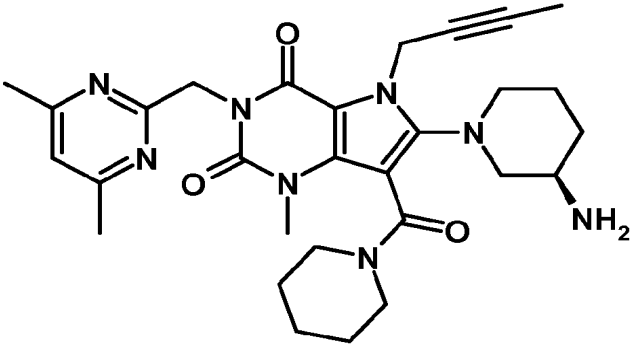
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| Compound | Structure |
|----------|-----------|
| (111) | |
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| (113) | |
| (114) | |
| (115) | |

| Compound | Structure |
|----------|--|
| (116) |  |
| (117) |  |
| (118) |  |
| (119) |  |

| Compound | Structure |
|----------|--|
| (120) |  |
| (121) |  |
| (122) |  |
| (123) |  |

| Compound | Structure |
|----------|--|
| (124) |  |
| (125) |  |
| (126) |  |
| (127) |  |

| Compound | Structure |
|----------|---|
| (128) |  |
| (129) |  |

Example 2 Coated tablets containing 75 mg of active substance

| | | |
|----|------------------------------|---------------|
| 5 | 1 tablet core contains: | |
| | active substance | 75.0 mg |
| | calcium phosphate | 93.0 mg |
| | corn starch | 35.5 mg |
| | polyvinylpyrrolidone | 10.0 mg |
| 10 | hydroxypropylmethylcellulose | 15.0 mg |
| | magnesium stearate | <u>1.5 mg</u> |
| | | 230.0 mg |

Preparation:

- 15 The active substance is mixed with calcium phosphate, corn starch, polyvinyl pyrrolidone, hydroxypropylmethylcellulose and half the specified amount of magnesium stearate. Blanks about 13 mm in diameter are produced in a tablet-

making machine and these are then rubbed through a screen with a mesh size of 1.5 mm using a suitable machine and mixed with the rest of the magnesium stearate. This granulate is compressed in a tablet-making machine to form tablets of the desired shape.

- 5 weight of core: 230 mg
 die: 9 mm, convex

The tablet cores thus produced are coated with a film consisting essentially of hydroxypropylmethylcellulose. The finished film-coated tablets are polished with beeswax.

- 10 Weight of coated tablet: 245 mg.

Example 3 Tablets containing 100 mg of active substance

Composition:

- 15 1 tablet contains:
- | | |
|-------------------------|---------------|
| active substance | 100.0 mg |
| lactose | 80.0 mg |
| corn starch | 34.0 mg |
| polyvinylpyrrolidone | 4.0 mg |
| 20 magnesium stearate | <u>2.0 mg</u> |
| | 220.0 mg |

Method of Preparation:

- 25 The active substance, lactose and starch are mixed together and uniformly moistened with an aqueous solution of the polyvinylpyrrolidone. After the moist composition has been screened (2.0 mm mesh size) and dried in a rack-type drier at 50°C it is screened again (1.5 mm mesh size) and the lubricant is added. The finished mixture is compressed to form tablets.

- 30 Weight of tablet: 220 mg
 Diameter: 10 mm, biplanar, facettted on both sides and notched on one side.

Example 4 Tablets containing 150 mg of active substance

Composition:

1 tablet contains:

| | | |
|----|----------------------|---------------|
| 5 | active substance | 150.0 mg |
| | powdered lactose | 89.0 mg |
| | corn starch | 40.0 mg |
| | colloidal silica | 10.0 mg |
| | polyvinylpyrrolidone | 10.0 mg |
| 10 | magnesium stearate | <u>1.0 mg</u> |
| | | 300.0 mg |

Preparation:

- 15 The active substance mixed with lactose, corn starch and silica is moistened with a 20% aqueous polyvinylpyrrolidone solution and passed through a screen with a mesh size of 1.5 mm.

The granules, dried at 45°C, are passed through the same screen again and mixed with the specified amount of magnesium stearate. Tablets are pressed from the

- 20 mixture.

Weight of tablet: 300 mg

die: 10 mm, flat

Example 5 Hard gelatine capsules containing 150 mg of active substance

- 25

1 capsule contains:

| | | |
|----|---------------------|------------------|
| | active substance | 150.0 mg |
| | corn starch (dried) | approx. 180.0 mg |
| | lactose (powdered) | approx. 87.0 mg |
| 30 | magnesium stearate | <u>3.0 mg</u> |
| | | approx. 420.0 mg |

Preparation:

The active substance is mixed with the excipients, passed through a screen with a mesh size of 0.75 mm and homogeneously mixed using a suitable apparatus. The finished mixture is packed into size 1 hard gelatine capsules.

Capsule filling: approx. 320 mg

Capsule shell: size 1 hard gelatine capsule.

Example 6 Suppositories containing 150 mg of active substance

1 suppository contains:

| | |
|---------------------------------------|-----------------|
| active substance | 150.0 mg |
| polyethyleneglycol 1500 | 550.0 mg |
| polyethyleneglycol 6000 | 460.0 mg |
| polyoxyethylene sorbitan monostearate | <u>840.0 mg</u> |
| | 2,000.0 mg |

Preparation:

After the suppository mass has been melted the active substance is homogeneously distributed therein and the melt is poured into chilled moulds.

Example 7 Suspension containing 50 mg of active substance

100 ml of suspension contain:

| | |
|--------------------------------|-----------|
| active substance | 1.00 g |
| carboxymethylcellulose-Na-salt | 0.10 g |
| methyl p-hydroxybenzoate | 0.05 g |
| propyl p-hydroxybenzoate | 0.01 g |
| glucose | 10.00 g |
| glycerol | 5.00 g |
| 70% sorbitol solution | 20.00 g |
| flavouring | 0.30 g |
| dist. water | ad 100 ml |

Preparation:

The distilled water is heated to 70°C. The methyl and propyl p-hydroxybenzoates together with the glycerol and sodium salt of carboxymethylcellulose are dissolved therein with stirring. The solution is cooled to ambient temperature and the active substance is added and homogeneously dispersed therein with stirring. After the sugar, the sorbitol solution and the flavouring have been added and dissolved, the suspension is evacuated with stirring to eliminate air.

5 ml of suspension contain 50 mg of active substance.

Example 8 Ampoules containing 10 mg active substance

1 ampoule contains:

| | | |
|------------------|--|---------|
| active substance | | 10.0 mg |
|------------------|--|---------|

| | | |
|-------------------------------|--|--|
| 0.01 N hydrochloric acid q.s. | | |
|-------------------------------|--|--|

| | | |
|------------------------|----|--------|
| double-distilled water | ad | 2.0 ml |
|------------------------|----|--------|

Preparation:

The active substance is dissolved in the necessary amount of 0.01 N HCl, made isotonic with common salt, filtered sterile and transferred into 2 ml ampoules.

Example 9 Ampoules containing 50 mg of active substance

1 ampoule contains:

| | | |
|------------------|--|---------|
| active substance | | 50.0 mg |
|------------------|--|---------|

| | | |
|-------------------------------|--|--|
| 0.01 N hydrochloric acid q.s. | | |
|-------------------------------|--|--|

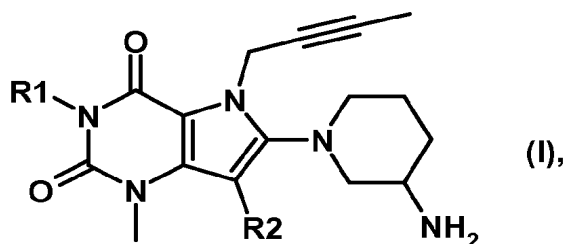
| | | |
|------------------------|----|---------|
| double-distilled water | ad | 10.0 ml |
|------------------------|----|---------|

Preparation:

The active substance is dissolved in the necessary amount of 0.01 N HCl, made isotonic with common salt, filtered sterile and transferred into 10 ml ampoules.

Patent Claims

1. Compound of formula (I)



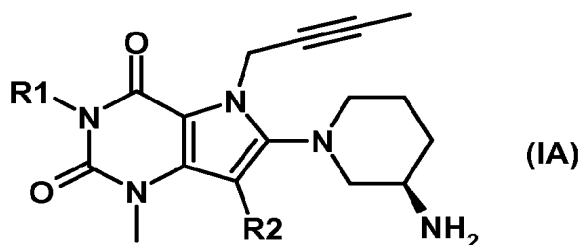
5 wherein R1 and R2 represent

R1: ([1,5]naphthyridin-2-yl)methyl, (quinazolin-2-yl)methyl, (quinoxalin-6-yl)methyl, (4-methyl-quinazolin-2-yl)methyl, 2-cyano-benzyl, (3-cyano-quinolin-2-yl)methyl, (3-cyano-pyridin-2-yl)methyl, (4-methyl-pyrimidin-2-yl)methyl, or (4,6-dimethyl-pyrimidin-2-yl)methyl and

R2: hydrogen, methyl; hydroxy, methoxy; cyano, carboxy, methoxycarbonyl; aminocarbonyl, methylaminocarbonyl, dimethylaminocarbonyl; (2-methoxyethyl)-aminocarbonyl, (2,2,2-trifluoroethyl)aminocarbonyl; cyclopropylaminocarbonyl, cyclobutylaminocarbonyl; (cyclopropylmethyl)aminocarbonyl, (cyclobutylmethyl)-aminocarbonyl; azetidin-1-ylcarbonyl, pyrrolidin-1-ylcarbonyl, piperidin-1-ylcarbonyl or morpholin-4-ylcarbonyl

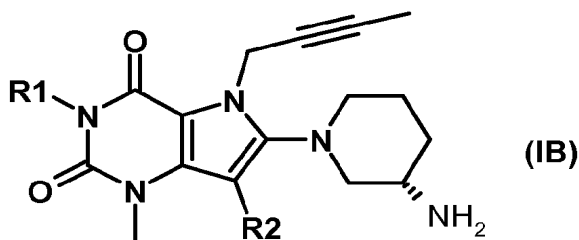
including the tautomers, enantiomers, diastereomers, mixtures and salts thereof.

2. Compound according to claim 1 of formula (IA)



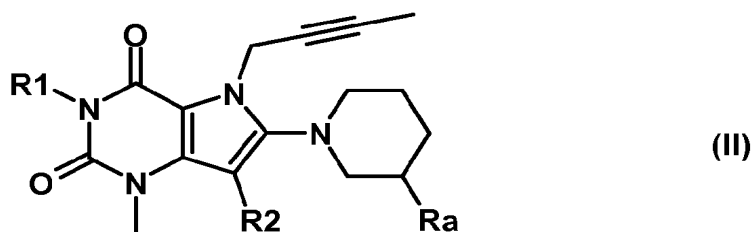
or (IB)

45



including the tautomers and salts thereof.

3. Intermediate products of formula (II)



wherein R1 and R2 have the same meanings as in claim 1 and Ra denotes an amino group protected by a protective group.

4. Compound according to one of claims 1 and 2, characterised in that the compound is a physiologically acceptable salt with an inorganic or organic acid.

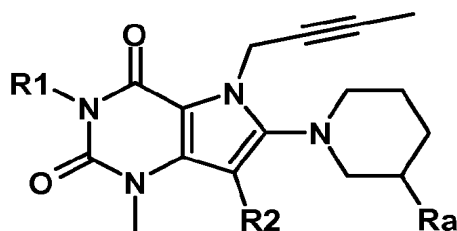
5. Medicament containing a compound according to one of claims 1 and 2 and one or more pharmaceutical adjuvants.

6. Use of a compound according to claims 1 to 4 for preparing a medicament for the treatment of type I and type II diabetes mellitus, arthritis, obesity, allograft transplantation and osteoporosis caused by calcitonin.

7. Process for preparing a compound according to claims 1 or 2, characterised in that

a compound of formula (II)

46



(II),

wherein R1 and R2 are defined as in claim 1 and Ra denotes an amino group protected by a protective group, is deprotected and then any protective groups which have been used during the reaction are cleaved.

8. Process according to claim 7, characterised in that the compounds of formula (I) thus obtained are resolved into their enantiomers or diastereomers.

9. Process according to claims 7 and 8, characterised in that the compounds of formula (I) thus obtained with inorganic or organic acids are converted into the salts thereof, particularly the physiologically acceptable salts thereof.

10. Process for the treatment of type I and type II diabetes mellitus, arthritis, obesity, allograft transplantation or osteoporosis caused by calcitonin, characterised in that a therapeutically effective amount of the compound of claim 1 or 2 is administered to a patient.

INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2007/058181

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07D487/04 A61K31/519 A61P7/12

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|-----------|---|-----------------------|
| Y | WO 2006/068163 A (DAINIPPON SUMITOMO PHARMA CO L [JP]; NAKAHIRA HIROYUKI [JP]; KIMURA HI) 29 June 2006 (2006-06-29) cited in the application claims 1,2,5-10,16-21; examples 14,48,49 & EP 1 829 877 A (DAINIPPON SUMITOMO PHARMA CO [JP]) 5 September 2007 (2007-09-05) | 1-10 |
| Y | WO 2005/085246 A (BOEHRINGER INGELHEIM INT [DE]; BOEHRINGER INGELHEIM PHARMA GM [DE]; HI) 15 September 2005 (2005-09-15) cited in the application Compounds (39), (52), (81), (82), (83) on pages 49 ff. as well as their protected derivatives (37), (50), (79) (80) on pages 21ff. and (2) and (5) on page 31; claims 1-8 | 1-10 |

☒ Further documents are listed in the continuation of Box C.☒ See patent family annex.

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Date of the actual completion of the international search

19 November 2007

Date of mailing of the international search report

28/11/2007

Name and mailing address of the ISA/

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Stroeter, Thomas

INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2007/058181

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|-----------|--|-----------------------|
| Y | <p>WO 2004/018468 A (BOEHRINGER INGELHEIM PHARMA [DE]; HIMMELSBACH FRANK [DE]; LANGKOPF ELK) 4 March 2004 (2004-03-04) cited in the application Compounds (55), (80), (81), (141), (142), (171), (246), (252) on pages 149ff; claims 1-22</p> <p>-----</p> | 1-10 |

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2007/058181

| Patent document cited in search report | | Publication date | Patent family member(s) | Publication date |
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| EP 1829877 | A | 05-09-2007 | AU 2005320134 A1 CA 2590912 A1 WO 2006068163 A1 | 29-06-2006 29-06-2006 29-06-2006 |
| WO 2005085246 | A | 15-09-2005 | AR 047614 A1 AU 2005219508 A1 BR PI0507873 A CA 2555050 A1 EP 1758905 A1 JP 2007522251 T KR 20070006780 A | 25-01-2006 15-09-2005 24-07-2007 15-09-2005 07-03-2007 09-08-2007 11-01-2007 |
| WO 2004018468 | A | 04-03-2004 | AU 2003253418 A1 BR PI0313648 A CA 2496249 A1 CN 1675212 A EP 1532149 A2 HR 20050157 A2 JP 2006503013 T KR 20050058375 A MX PA05001684 A | 11-03-2004 08-05-2007 04-03-2004 28-09-2005 25-05-2005 31-05-2006 26-01-2006 16-06-2005 19-04-2005 |